CLINICIAN

Vol. 20 No. 1 ISSN 0264-6404 March 2002

The National Institute of Neurological Disorders and Stroke

of the

National Institutes of Health

Presents

Evolving Directions in the Management of Epilepsy

Jointly sponsored by the University of Cincinnati and SynerMed Communications

in cooperation with the American Epilepsy Society, American Academy of Neurology, and Epilepsy Foundation

This program is made possible by an educational grant provided by Ortho-McNeil Pharmaceutical, Inc.

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Evolving Directions in the Management of Epilepsy

Release Date: March 2002

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CME ACCREDITATION INFORMATION

Method of Participation: The program consists of a 32-page monograph with a CME Post-Test/Program Evaluation.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati College of Medicine and SynerMed Communications. The University of Cincinnati College of Medicine is accredited by the ACCME to sponsor continuing medical education for physicians.

This educational activity has been made possible through an educational grant from Ortho-McNeil Pharmaceutical, Inc.

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The University of Cincinnati College of Medicine designates this continuing medical education activity for up to 3 credit hours in Category 1 of the Physician's Recognition Award (PRA). Each physician should claim only those hours of credit that he/she actually spent in this educational activity.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, the clinician will be able to:

- Identify the consequences of epilepsy and its treatment.
- Discuss the role of prevention, disease modification, and neuroprotection in treatment.
- Review older and newer AEDs in terms of safety, efficacy, and tolerability.
- Describe the decision-making process for initiating and withdrawing AED therapy.
- Select AEDs for different patient populations.
- Identify surgical candidates among adult and pediatric patients.

TARGET AUDIENCE

Neurologists, epileptologists, internists, and pediatricians who manage patients with epilepsy.

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Introduction

The consequences of epilepsy are becoming increasingly appreciated. Patients with epilepsy experience a higher risk of death and are more prone to sustain injuries and trauma than the general population. Epilepsy can impose special challenges for those individuals who have the disorder, such as quality-of-life issues, maintaining their independence, relationships, or keeping a job. Furthermore, the quality of life for people with epilepsy is often impaired by the stigma many in our society still associate with a diagnosis of epilepsy, as well as the fear of other's reactions, shame, and loneliness felt by patients with epilepsy. These concerns must be addressed by the clinician and patient, and they must be incorporated into the treatment options/decisions.

Complete seizure control is the goal of epilepsy treatment. Approximately 60% of persons with epilepsy achieve seizure freedom through antiepileptic drug (AED) therapy. Surgical management may be an option for some patients with certain kinds of difficult-to-control seizures, as demonstrated by a recent study that found that surgery for these patients produced significantly better results than continued treatment with medication.[1]

The success rate for seizure freedom was achieved using traditional AEDs, which often have tolerability and toxicity problems. However, during the past decade, research has improved the prospects both for accurate diagnosis and successful treatment. New AEDs have been introduced that offer comparative efficacy and also better tolerability and fewer side effects than the traditional AEDs. More patients should be able to attain seizure freedom not only as a result of the improved understanding of the classification of seizure types and epilepsy syndromes but also because of the greater variety of therapeutic options.

The term "epilepsy" refers to a wide range of disorders with differing etiologies, natural histories, and prognoses. The unifying characteristic of all the epileptic disorders is the presence of recurrent, unprovoked seizures. Although this definition covers many disparate disorders, it excludes seizures immediately following an identifiable proximate cause, such as febrile seizures, acute symptomatic seizures caused by alcohol withdrawal, or acute posttraumatic seizures. Febrile seizures occur during a sudden rise in temperature early in the course of an illness. As many as 5% of infants and young children will experience febrile seizures; in approximately two thirds of cases there will be no recurrence. This monograph will address the term "epilepsy" in its broadest sense, including all recurrent unprovoked seizures but excluding provoked seizure types.

Classification of the Epilepsies and Epileptic Syndromes

The current framework for the classification of the epilepsies and those clusters of features that may be considered to be epileptic syndromes was proposed by the International League Against Epilepsy (ILAE) in 1985 and revised in 1989 (Tables 1 and 2). The International Classification of Epilepsies and Epileptic Syndromes (ICE) classifies the epilepsies based on careful history and neurologic examination, etiology, a hereditary disposition, genetics, age of onset, and clinical and electroencephalographic (EEG) characteristics. Each of the major syndrome categories subsumes a range of seizure types and epileptic syndromes with different presentations, etiologies, and prognoses.

Although the ILAE classification scheme is useful, it has its shortcomings. In a population-based incidence study, patients were placed in each category according to the ILAE classification.[2] Of 804 patients who were evaluated, only 33.6% were in diagnostic ILAE categories, while 66.4% were in various nonspecific categories. Only 24% of the localization-related epilepsies could be clearly identified as to site of origin. Many of the well-characterized epilepsy syndromes (eg, West syndrome, Lennox-Gastaut syndrome, early myoclonic encephalopathy) were not represented in this patient group.[2] This study illustrates the difficulty of creating a classification for all seizure types and epilepsy syndromes and points to the complexity of making a precise and accurate diagnosis of seizure disorders. The ILAE guidelines are currently under revision but the expected publication date is currently unknown.

Table 1

INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES

Partial seizures (beginning locally)

- Simple partial seizures (without impaired consciousness)
  - Motor symptoms
  - Somatosensory or special sensory symptoms
  - Autonomic symptoms
  - Psychological symptoms
- Complex partial seizures (with impaired consciousness)
  - Simple partial onset followed by impaired consciousness
  - Impaired consciousness at onset
- Partial seizures evolving into secondary generalized seizures

Generalized seizures (convulsive or nonconvulsive)

- Absence seizures
  - Typical
  - Atypical
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Myoclonic seizures
- Atonic seizures

Unclassified seizures

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Recent Epilepsy Research

Several areas of epilepsy management have benefited from recent research developments, including diagnostic techniques such as neuroimaging, an improved understanding of the genetic factors and mechanisms of epileptogenesis, and the advent of several new AEDs, which allow for more therapeutic options to achieve seizure control. A better understanding of these recent developments in research will help clinicians to treat and manage their patients with epilepsy more successfully.

Neuroimaging

Magnetic resonance imaging (MRI) has rapidly become the method of choice in diagnosing epilepsy since it is more sensitive than computed tomography (CT). It is accurate in detecting small tumors, cortical dysgenesis, mesial temporal sclerosis (MTS), and focal gliosis. The optimal MRI technique when evaluating the temporal lobe is acquisition of many thin coronal slices through the temporal region, employing fluid-attenuated inversion recovery (FLAIR) images.[3]

Other advances include positron emission tomography (PET) and single photon emission computed tomography (SPECT), which are useful techniques in identifying the precise localization of lesions in surgery candidates. Abnormalities in both metabolism and perfusion can be detected in subtle focal lesions at baseline and also in the postictal state.

Genetic Factors in Epilepsy

Epilepsies that are currently known or thought to have genetic etiologies include both localization-related and generalized epilepsies. Forms of inheritance of epilepsy syndromes can be autosomal dominant (AD), autosomal recessive (AR), complex, or mitochondrial. Table 3 (page 8) lists some inherited epilepsies.

Genetic etiologies are especially important in epilepsies affecting infants and young children. Many epilepsies currently labeled as idiopathic may be found to have a genetic etiology. In some epilepsies with environmental causes, such as seizures secondary to head injury, genetic factors may increase the patient's susceptibility. Moreover, many of the diseases or conditions associated with epileptic seizures have genetic or metabolic components.

An area of research that holds much promise is the identification of individuals who are at increased risk for developing idiosyncratic reactions to AEDs. While dose-related drug reactions occur in a predictable fashion in the general population, only a small percentage of patients with epilepsy will exhibit idiosyncratic adverse events with some AEDs. It is likely that genetic factors may play a role in susceptibility to idiosyncratic reactions, and identification of these factors will permit better individualization of AED treatment.[4]

Mechanisms of Epileptogenesis

Improved understanding of the mechanisms of epileptogenesis, particularly the role of the neurotransmitters and signaling pathways, is essential to advance new AED development. Traditional AEDs block the voltage-gated Na+ channel or increase the transmission of γ-aminobutyric acid (GABA).[5] However, these drugs are anticonvulsant but not necessarily antiepileptogenic. Furthermore, higher serum concentrations of conventional AEDs impair cognitive functioning, as these agents block a necessary component of normal neurotransmission. An improved understanding of cellular mechanisms of epileptogenesis and seizures will reduce such adverse effects on neurotransmission.

A number of components of neuronal excitability have more recently been identified as potential targets for anticonvulsant and antiepileptogenic actions. Important new research is aimed at evaluating not just mechanisms underlying ictal activity but also mechanisms of epileptogenesis. Disease modification, in this case to prevent the progression of epilepsy in an individual at risk, is becoming the focus of basic epilepsy research. The role of Ca++ ions in the control of neuronal excitability has been the focus of increasing attention. Although the role of the T-type Ca++ channel has been understood for some time, two other Ca++ channels—the L-type and the N-type—also are being investigated. AEDs that target those channels are considered likely to have broader antiepileptic actions.[6] There is evidence that although *N*-methyl-D-aspartate (NMDA) is associated with increased neuronal excitability, it is not essential for the expression of fully kindled seizures. In addition, agents that address the kainic acid (KA) or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor as well as the NMDA receptor are particularly promising for the treatment of recurrent seizures.[5]

Epilepsy is highly prevalent in the immature brain, with the first year representing one of the periods in life of highest incidence for seizures.[7] While ion channels and neurotransmitter receptors make good targets for treatment in the mature brain, an important issue is that these targets play critical roles in normal brain development and undergo dramatic changes during maturation. These include the expression of excitatory and inhibitory neurotransmitter systems, ion channels, neurotransmitter transporters, and brain metabolism.[8] Hence, different therapeutic strategies must be considered for the immature brain compared with the mature brain.

New AED Options

Eight new AEDs have been approved since 1993, and more are currently in development. One important difference between the traditional AEDs and the newer agents is that generally the newer agents have a broader range of targets, including not only Na+ channel blockade and GABA potentiation but also Ca++ activity and glutamatergic inhibition. Potentially, AEDs that have multiple mechanisms of action may be effective in treating a broader spectrum of seizure types and epileptic syndromes. Additional advantages of the newer AEDs are that, as a group, they are generally better tolerated and have fewer drug-drug interactions.

Epidemiology, Natural History, and Consequences of Epilepsy

In the United States, the annual incidence of epilepsy (a measure of newly occurring epilepsy over time) is 40 to 50 cases per 100,000 population. The overall prevalence of epilepsy (a measure of the number of epilepsy cases in the population at a particular point in time) in the United States

Table 2

INTERNATIONAL CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

- Localization-related (focal, local, or partial) epilepsies and syndromes (eg, benign childhood epilepsy with centrotemporal spikes, rolandic)
- Generalized epilepsies and syndromes:

Idiopathic	Cryptogenic or Symptomatic
Benign myoclonic epilepsy in infancy	Infantile spasms
Childhood absence epilepsy	Lennox-Gastaut syndrome
Juvenile absence epilepsy	Early myoclonic encephalopathy
Juvenile myoclonic epilepsy	Early infantile epileptic encephalopathy
Generalized tonic-clonic seizures on awakening	
Adult myoclonic epilepsy	

- Epilepsies and syndromes with both generalized and focal seizures (eg, neonatal seizures)
- Epilepsies without unequivocal generalized or focal features
- Special syndromes (eg, febrile convulsions)

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Table 3
INHERITED FORMS OF EPILEPSY

Syndrome	Inheritance	Comments
Benign childhood epilepsy with centrotemporal spikes (BECTS)	AD	Occurs in siblings
Nocturnal frontal lobe epilepsy	AD	Affects nicotinic acetylcholine receptors
Benign familial neonatal convulsions	AD	Affects K+ channels
Childhood absence epilepsy	Complex	May affect Ca++ channels
Juvenile absence epilepsy	Complex	
Juvenile myoclonic epilepsy	Complex	May affect Ca++ channels
Unverricht-Lundborg syndrome	AR	Affects noncaspase cysteine protease inhibitor
Generalized epilepsy with febrile seizures	AD	Affects voltage-gated Na+ channel GABA site implicated

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is 6 to 7 per 1000 population.[9] Figure 1 shows that the incidence of unprovoked seizures in developed countries varies widely with age. Although there are differences among the countries, the overall trend is similar. The incidence is well over 100 per year per 100,000 in the first few years of life, declines to below 50 per year per 100,000 in the years between 20 and 60, and then climbs steeply once again starting around age 65, exceeding 150 per year per 100,000 by age 75.[9-12]

The etiology of epilepsy varies substantially with age. For all age cohorts, approximately 65% of cases are of unknown origin. The incidence of idiopathic epilepsies declines to 48% in the elderly, with the single most common etiology, stroke (cerebrovascular accident), accounting for 32% of epilepsies. Other important etiologies in the elderly include degenerative conditions, eg, Alzheimer's disease; 10% of persons with Alzheimer's disease develop epilepsy.[7] In children, the most frequently identified cause of epilepsy is congenital (eg, neuronal migration disorders), accounting for approximately 20% (Table 4).[7]

The incidence of seizure types varies across age groups. Generalized-onset seizures, including generalized tonic-clonic (GTC), absence, and other types, are the most common seizure types in childhood. Generalized-onset seizures account for approximately 43% of all seizures sustained through the first 5 years of life. The percentage of GTC seizures remains relatively constant in terms of incident cases for each age group, while other generalized-onset seizure types (such as absence seizures) decline with advancing age. The incidence of complex partial-onset seizures, however, increases markedly from childhood (approximately 24%) through adulthood (approximately 40%) to age 65 or older (approximately 50%).[7]

Causes of Epilepsy

Risk factors for epilepsy also are age-dependent. The risk for childhood epilepsy is increased by mental retardation, cerebral palsy, infections of the central nervous system (CNS), and history of febrile seizures or convulsions. Although the great majority of children who have febrile seizures do not develop epilepsy, 11 of 1000 children with simple febrile convulsions will develop epilepsy by age 7. Adverse events during the prenatal months and during birth, including prematurity and low birth weight, do not appear to be independent predictors of epilepsy. However, a high percentage (39.9%) of children with epilepsy have been found to have an additional neurologic deficit.[13]

Risks for developing epilepsy have been clearly identified through population studies, and Figure 2 (page 10) shows the odds ratio for risk factors on a logarithmic scale for epilepsy in adults. No risk, at the bottom of the graph, has an odds ratio of 1. By far, the greatest risk factor for epilepsy is military head injury, with an odds ratio of 580 during the first 12 months after the injury for Vietnam veterans who survived penetrating head wounds. The odds ratio of developing epilepsy was 25 as long as 10 to 15 years after the injury. Other factors with high odds ratios are severe civilian head injury (29), stroke (20), encephalitis (16), Alzheimer's disease (10), untreated left ventricular hypertrophy (7.3), bacterial meningitis (4), multiple sclerosis (4), depression (3.7), and alcohol or heroin use (3). Pharmacologically treated left ventricular hypertrophy appears to reduce the risk of developing epilepsy, with an odds ratio of 0.7.[13]

Stroke is a risk factor for epileptic seizures. It has been assumed that the cerebrovascular event creates an epileptogenic lesion that serves as a focus for seizures; thus, only unprovoked focal or partial-onset seizures should occur after stroke. However, this is not the case and generalized-onset seizures often occur after stroke, suggesting that persistent global alterations in neurotransmitter function also may be factors in epileptogenesis. There also is evidence that risk factors for stroke may increase the risk for seizures; the prevalence of epilepsy preceding stroke was 4.55% compared with 0.6% in a population of matched controls.[13]

Severe head injuries are an important cause of epilepsy at all stages of life because they occur with increased frequency in early childhood, in the young adult years, and in old age. One type of seizure often associated with patients with head injuries is acute symptomatic seizures; these occur in direct proportion to the severity of damage to the brain. However, children are more likely than adults to experience convulsions in association with head injuries.[7]

Consequences of Epilepsy

Overall, patients with epilepsy are at a significantly increased risk of death. The mortality rate is two to three times that of the general population, attributable both to epilepsy itself and to some underlying diseases resulting in epilepsy (eg, brain lesions, cerebrovascular conditions).[14] Patients with epileptic seizures are subject to more trauma, including head injury, burns and scalds, and dental injuries. These are linked with seizure frequency and severity, with a significantly higher frequency in patients who sustain more than one seizure per month. The seizure type most often linked with trauma is the drop attack.[15] The most common consequence directly attributable to epilepsy is death during status epilepticus, fatal accidents during seizures, suicide, and sudden unexplained death in epilepsy (SUDEP). Status epilepticus, defined as continuous clinical or electrical seizure activity or repetitive seizures with incomplete neurologic recovery interictally for at least 30 minutes, is estimated to be associated with 22,000 to 42,000 deaths in the United States annually.[16]

Sudden Unexplained Death in Epilepsy

The most common category of seizure-related death is SUDEP, defined as “sudden unexpected, witnessed or unwitnessed, nontraumatic, nondrowning deaths in patients with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, with necropsy not revealing any toxicological or anatomical cause of death.”[17] Seven percent to 17% of deaths in persons with epilepsy are attributed to SUDEP.[18,19] The risk of sudden unexplained death in persons with epilepsy is 24 times higher than the risk of sudden unexplained death in the general population (Table 5, page 10).[18]

Figure 1
INCIDENCE OF UNPROVOKED SEIZURES: SELECTED STUDIES

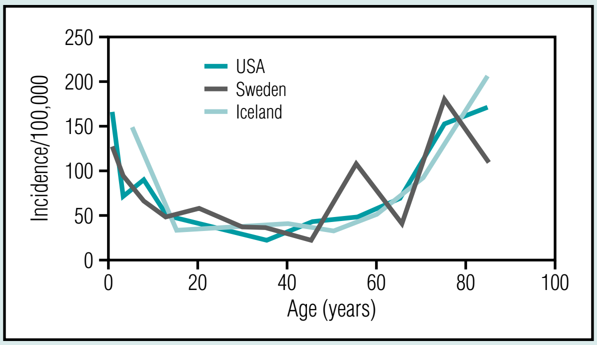

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Table 4
CAUSES OF EPILEPSY

Causes may be divided into 3 groups for which mechanisms and prognoses are different:

- Cerebral palsy, mental retardation, and migration disorders
- Genetics
- Postnatally acquired neurologic insults
  - Progressive conditions

Postmortem studies of SUDEP cases have found a pathologic substrate for the epilepsy in 34% to 70% of cases.[14] The risk of SUDEP increases with markers for increased severity, the highest incidence being found in surgical candidates and especially in surgical failures. Higher sudden death rates also are found in populations of patients with intractable epilepsy, suggesting that the risk of SUDEP is related to seizure control.[14] SUDEP rates are higher during the young adult years, and may be more common in males than in females with epilepsy.[18] The rates of SUDEP are greater in patients referred to specialty epilepsy centers than in the epilepsy-prevalent population, and even greater in patients with complex partial epilepsies enrolled in clinical trials of adjunctive AEDs or patients receiving vagal nerve stimulation.[20]

There is no definitive evidence linking any particular AED with increased SUDEP rates, although it has been noted that the proportion of SUDEP patients taking carbamazepine is higher than the proportion taking this agent in the rest of the population of persons with epilepsy. There also are anecdotal reports linking carbamazepine use with sinus arrest and bradyarrhythmia.[14] Changes in AED therapy and poor compliance also have been linked with increased rates of SUDEP. Other factors that may increase the risk of SUDEP are neurologic deficits and learning disabilities, which may be markers for increased epilepsy severity. Overall, the evidence suggests that SUDEP is a seizure-related event, confirming the primacy of seizure control as the goal of epilepsy treatment.[14]

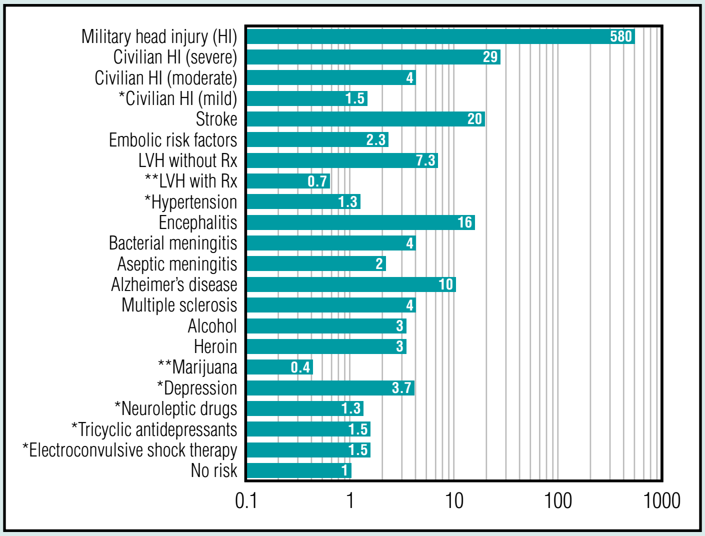
Economic, Social, and Psychological Obstacles

Death and physical trauma are by no means the only adverse consequences experienced by patients with epilepsy. These individuals also are subject to a wide range of economic, social, and psychological problems and obstacles. Patients with epilepsy are less likely to be married than individuals in the general population, and approximately 30% believe that epilepsy affects their relationships with others, such as a spouse, partner, or their children.[21] Patients with epilepsy often have lower educational attainment and live in lower-income households than the general population. Nearly 40% of patients with epilepsy believe that epilepsy adversely affects their quality of life. For many respondents, fear and uncertainty were labeled as the worst aspects of having epilepsy.[21]

Patients with epilepsy are often unemployed or have difficulty keeping a job. According to a survey conducted in the mid-1990s, only 24% of those with epilepsy were employed full-time, and 25% were unemployed. The unemployed fraction did not include students, homemakers, or retired persons. Seventeen percent of those surveyed agreed that epilepsy affected their job performance, and 7.7% indicated that the worst aspect of epilepsy was difficulty in maintaining employment. Approximately two thirds of the patients attributed unemployment to the epilepsy. The specific reasons cited included their employers' fears of liability, difficulty in getting transportation to the job, and stigma.[21]

Figure 2

RISK FACTORS FOR EPILEPSY



*Not significant, ** Protective, LVH – Left ventricular hypertrophy

Adapted with permission from Hessdorffer DC, Verity CM. Risk factors. In: Engle J, Jr, Pedley TA, eds. *Epilepsia: A Comprehensive Textbook*. Philadelphia, Pa: Lippincott-Raven Publishers. 1997:62.

Another adverse effect of epilepsy was performance in school (54%); the second adverse event reported was cognitive function. Between 40% and 50% agreed that several areas of cognitive performance were adversely affected by epilepsy (or its neurologic problems and treatments). These areas included memory, concentration, thinking clearly, and emotional well-being.[21]

Driving an automobile is a key concern for patients with epilepsy. More than 10% of those surveyed identified the inability to drive a car as the worst thing about having epilepsy, and 36% agreed that having epilepsy affected their ability to drive. Nine percent reported that having a seizure had caused them to have an automobile accident.[21]

Quality of life for persons with epilepsy may be related to seizure frequency. A study of 139 patients determined that adults with epilepsy who have been seizure-free for as little as 4 weeks can attain a quality of life that is comparable with that of the general population. In contrast, patients who had sustained seizures in the preceding 4 weeks reported significantly decreased quality of life than seizure-free patients and the general population. Patients who had sustained six or more seizures were worse than patients who had sustained five or fewer seizures. The study employed an instrument, the Medical Outcomes Study Short Form-36, that evaluates eight different domains of health-related quality of life, including both physical and mental health.[22]

The economic costs of epilepsy have been calculated based on incidence and prevalence estimates, medical and surgical costs, and indirect costs such as lost earnings and lost productivity. The total cost (in 1995) has been estimated at approximately $1.7 billion, and the total projected indirect annual cost has been estimated at approximately $10.8 billion, for a total annual cost of approximately $12.5 billion.[23] The largest shares of costs were physician and hospital services (approximately 40%) and drug treatment (approximately 30%). Diagnostic procedures and surgery accounted for approximately 13% and approximately 6%, respectively (Figure 3). A 6-year follow-up of 608 cases in two medical centers revealed a pattern: Over the 6-year period, the average cost per case was approximately $6500; however, costs declined sharply from approximately $2650 in the first 3 months to approximately $325 for the whole of year 6. This dramatic decline reflects both the intense service use for diagnosis

Table 5

SUDEP: POTENTIAL RISK FACTORS

- Epilepsy severity
- Seizure type
- Gender
- Age at onset
- Etiology of epilepsy
- Noncompliance
- Specific therapeutic regimen

and initial treatment and the relatively high percentage of patients with epilepsy who achieve seizure freedom with initial treatment.[23]

Diagnostic Issues

The precise and accurate diagnosis of epilepsy is difficult. One of the major obstacles to diagnosis is that most epileptic seizures are unwitnessed. They tend to be brief and transient, and they occur unpredictably.[24] Descriptions of the event by an observer are likely to be inaccurate, especially if the patient lost consciousness. A first step in the diagnosis is to determine whether an epileptic seizure occurred, or if it was caused by some immediate correctable condition such as a provoked or reflex anoxic event. Single seizures with identifiable proximate causes are not epileptic and will not require AED therapy.[3]

A careful description of the seizure is needed for classification of the seizure phenotype. The clinician needs to know what the seizure looked like and how long the seizure lasted. Further evidence may be obtained from an EEG. However, as many as 50% of patients with epilepsy do not show any EEG abnormalities on a routine trace.[3] Techniques that may increase the yield of abnormalities are the 24-hour ambulatory EEG, EEG performed after sleep deprivation, and video recording of seizures.[3,24]

Neuroimaging is essential for both diagnostic and prognostic information. The ILAE has recommended that all patients with new cases of localization-related (partial-onset) epilepsies be studied using MRI rather than CT. While the sensitivity of CT for identification of epileptogenic lesions is between 30% and 50%, the sensitivity of MRI is between 50% and 97%.[25]

In addition to its superior sensitivity and specificity, MRI permits visualization of brain structures in multiple slices without the need for ionizing radiation. The bony artifacts that sometimes degrade the CT image are not important factors in MRI. The contrast agents needed for CT scans are not necessary in MRI. Moreover, CT studies in several types of epilepsies, including MTS, are often normal, revealing no epileptogenic foci.[25]

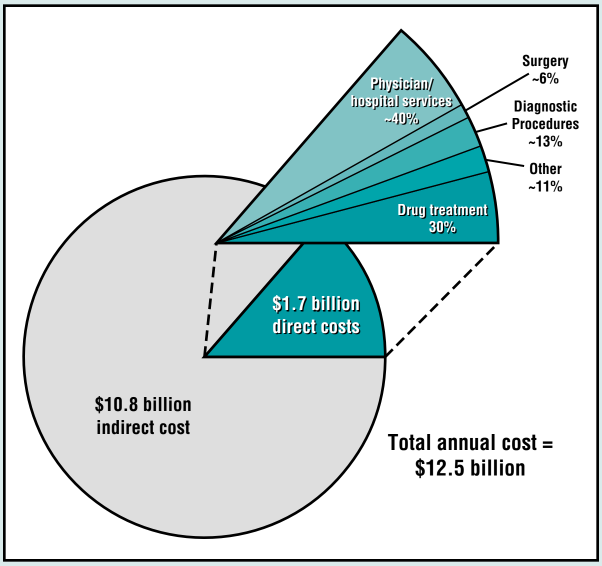
In contrast, MRI is generally considered to be a reliable indicator of MTS in patients with partial epilepsies. Formerly, these lesions could be identified only during pathologic examination. MRI also is a reliable and accurate indicator of several other lesions, such as tumors, vascular malformations, and neuronal migration disorders. Patients with accurately identified and precisely localized lesional epileptic syndromes are excellent candidates for surgery. A Mayo Clinic study in 23 patients with intractable epilepsy associated with lesional pathologies found that 56% of the patients were seizure-free after surgery, and approximately three quarters of the patients had a greater than 80% reduction in seizure frequency.[25]

Other neuroimaging techniques of importance in candidates for surgery are PET and SPECT. These allow images to be constructed in coronal, transverse, and sagittal planes, as well as in three dimensions, facilitating precise localization of lesions that are targets for surgery.[26]

One of the epilepsy syndromes that appears to be especially subject to misdiagnosis is juvenile myoclonic epilepsy (JME). This syndrome is characterized by typical absence seizures, myoclonic jerks, and GTC seizures. It is often age-related (onset from 8 to 30 years; mean, 14 years) and accompanied by a normal physical examination and CT brain scan, with typical generalized spike-wave and poly-spike-wave abnormalities on EEG tracing.[27] Treated with the appropriate AEDs, 80% to 85% of patients with JME can achieve seizure freedom.[28,29] The consequences of misdiagnosis can be significant, including status epilepticus, injury, and loss of employment.[24]

Generalized epilepsy may be misdiagnosed as partial epilepsy. A study identified 16 patients with generalized epilepsy who had previously been diagnosed with localization-related epilepsy.[30] Various causes were attributed to this misdiagnosis, including the failure to identify characteristic epileptiform abnormalities on EEG tracings. Other causes included the inability to base the diagnosis on syndrome characteristics. It also was suggested that a bias exists in favor of diagnosing patients

Figure 3
THE ECONOMIC COSTS OF EPILEPSY



Adapted with permission from Begley CE, Famulari M, Annegers JF, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia.* 2000;41(3):342-351.

with partial-onset rather than generalized epilepsies since there are more treatment options available for partial epilepsies. Some of these options include participation in AED trials and surgical intervention.[30]

Medical Management Issues

Initiation of Therapy

The ultimate goal of treatment for the epilepsies is the preservation of quality of life by complete seizure control. In general, patients who have sustained only a single seizure or whose seizures are widely separated should not routinely be given prophylactic AEDs. There may be exceptions such as patients who have an underlying structural abnormality or those who have a high-risk epilepsy syndrome such as JME; these patients should be treated after a single confirmed event.[3]

Guidelines have been developed to assist the clinician in deciding on when to initiate treatment in a patient after a first seizure (Table 6). Even within these guidelines, consideration should be given to the individual circumstances of each patient.[31] In each case the risk of seizure recurrence should be weighed against the risk of chronic administration of an AED.

Risk of Seizure Recurrence

The practitioner must assess the risk of seizure recurrence to optimally manage patients with epilepsy. Numerous studies have examined the risk of recurrence after an initial seizure. Overall, approximately 35% of persons who have sustained a first unprovoked seizure can be expected to have a second seizure within 3 to 5 years. The estimated risk of recurrence, however, varies between 20% and 100%, depending on clinical characteristics. The decision whether to initiate AED treatment after a single unprovoked seizure will depend on the individual patient's specific circumstances. However, a single unprovoked seizure does not require initiation of AED treatment in most cases. The risk of recurrence after a second unprovoked seizure is greater. A study of 204 patients who had sustained a single unprovoked seizure found that 63 (31%) had a second seizure, and of these, 41 (65%) had a third seizure. Not only did the likelihood of recurrence increase, but also the recurrences are likely to occur closer together. Approximately 75% of persons who have two or three unprovoked seizures will have additional seizures within 4 years. Factors increasing the risk are history of neurologic insult or other remote symptomatic etiology. These data suggest that, in contrast with persons who have sustained a single seizure, persons who have had second or third unprovoked seizures should be treated.[32]

There is evidence that the underlying cause of the epilepsy is a major prognostic factor for recurrence. In general, patients with generalized epilepsy achieved seizure freedom more easily than those with partial epilepsy. In one study of 2200 adult outpatients, 82% of patients with generalized idiopathic epilepsy were able to achieve seizure freedom for more than 1 year. This contrasted with the 11% to 45% of patients with partial epilepsies, whether symptomatic or cryptogenic, who achieved seizure freedom. In particular, only 11% of patients with hippocampal sclerosis were able to achieve seizure freedom.[33]

If the decision is to initiate AED therapy, the selection of the first AED is based on several factors: the seizure type or epilepsy syndrome; the safety of the AED in conjunction with the age and sex of the patient; the spectrum of activity of the AED (especially if the cause is unknown); the side-effect profile of the AED; and the patient's probable capacity to tolerate the side effects at the therapeutic dose. A complete discussion of AED safety and efficacy follows.

Table 6
WHEN TO START TREATMENT WITH AEDs AFTER A SINGLE SEIZURE

Definitely

- With structural lesion
  - Brain tumor, such as meningioma, glioma, neoplasia
  - Arteriovenous malformation
  - Infection, such as abscess, herpes, encephalitis
- Without structural lesion
  - History of epilepsy in sibling (but not parents)
  - EEG with definite epileptic pattern
  - History of previous symptomatic seizure (seizure in the context of an illness or a childhood febrile seizure)
  - History of previous brain injury, stroke, CNS infection, significant head trauma
  - Status epilepticus at onset

Possibly

- Unprovoked seizure with none of the above risk factors

Probably not (although short-term therapy may be used)

- Alcohol withdrawal
- Drug abuse
- Seizure in context of acute illness (ie, high fever, dehydration, hypoglycemia)
- Postimpact seizure (single seizure immediately after an acute blow to the head)
- Specific benign epilepsy syndrome, such as febrile convulsions or benign epilepsy with centrotemporal spikes
- Seizure provoked by excessive sleep deprivation (eg, college student at examination time)

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Response to Therapy After Failure of First AED

There is mounting evidence that, regardless of which AED is selected first, the response to succeeding AED regimens is sharply lower. In a trial of 470 patients with previously untreated epilepsy (Table 7), 47% responded to the first AED and 44% were seizure-free during continued therapy with the first AED. Of those patients who experienced failure with the first AED, only 13% responded to the second AED, and 9% were seizure-free during continued therapy. In those patients who showed no change with the second AED, only 1% were seizure-free during monotherapy with a third AED, and 3% were seizure-free during therapy with two AEDs.[34] Of patients who experienced inadequate seizure control with the first AED, only 16% were able to achieve seizure freedom with any subsequent AED. Patients who failed the first AED because of intolerable side effects were able to achieve seizure freedom with a subsequent AED 32% of the time, and those who experienced idiosyncratic reactions were able to achieve seizure freedom with a subsequent AED 38% of the time.[34]

Monotherapy Versus Polypharmacy

Many factors need to be considered in deciding whether to prescribe a second or third AED as monotherapy or to move to polypharmacy. At this time there is no conclusive evidence favoring one approach over the other. However, in the previously mentioned study, several drug combinations were used, and 36% of patients became seizure-free when the combination included a sodium channel blocker such as carbamazepine, phenytoin, or lamotrigine, in combination with an AED having multiple mechanisms of action, such as valproate, gabapentin, or topiramate. None of the patients who received a sodium channel blocker in combination with a pure GABA agonist, such as vigabatrin or tiagabine, became seizure-free.[34] These conclusions should be viewed as preliminary because the study was retroactive and not double-blind.

Lack of response to the first AED may imply that the patient has refractory epilepsy. It has been suggested that some patients have refractory epilepsy at the onset, rather than developing this disease over time. These patients are likely to have structural brain abnormalities and to have sustained more than 20 seizures before treatment is initiated. Such patients may be identified as candidates for surgery or for polypharmacy.[34]

AED polypharmacy has several drawbacks. AED combinations can cause interactions like hepatic enzyme reduction or inhibition, altered protein binding, or additive adverse effects from pharmacokinetic or pharmacodynamic interactions. It has been suggested that moving to polypharmacy too soon does not allow for sufficient evaluation of the effects of monotherapy. Finally, it has been observed that certain AED combinations have resulted in an increase in seizure frequency.[35]

Table 7

SUCCESS OF AED REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY

Variable	No.	%
Response to first drug	222	47
Seizure-free during continued therapy with first drug	207	44
Remained seizure-free after discontinuation of first drug	15	3
Response to second drug	61	13
Seizure-free during monotherapy with second drug	41	9
Remained seizure-free after discontinuation of second drug	20	4
Response to third drug or multiple drugs	18	4
Seizure-free during monotherapy with third drug	6	1
Seizure-free during therapy with two drugs	12	3
Total	301	64

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AED combinations can be effective, especially if several considerations are taken into account (Table 8). Combinations focused on minimizing drug-drug interactions can be evaluated based on a knowledge of AED pharmacokinetics, binding sites, specific hepatic or renal metabolism modes, and routes of elimination. Combinations chosen by their mechanisms of action can now be employed based on an understanding of the paths of neurotransmission targeted by AEDs. Combinations based on adverse effects aim to utilize drugs with different adverse-effect profiles (eg, avoid AED combinations in which both drugs are highly sedative or both cause weight gain).

Maintenance Therapy

Once seizure control has been attained, whether through monotherapy or polypharmacy, the clinician's task is to manage the patient's therapy for the long term. Some

Table 8

TRADITIONAL AED POLYPHARMACY: SELECTION FACTORS

- Non-additive adverse effects
- Spectrum of activity
- No or manageable pharmacokinetic interactions
- Mechanism of action
- Low-dose polytherapy
- Intermittent/rescue treatment (benzodiazepines)

patients discontinue taking AEDs after a few years of complete seizure freedom, while others continue taking AEDs for decades. Factors that contribute to successful long-term therapy include compliance, minimizing side effects, and maintenance of optimal serum levels. These factors are often interrelated, eg, patients who have difficulty tolerating an AED are more likely to be noncompliant, and lack of compliance leads to fluctuating serum levels, which, in turn, adversely affect the therapeutic efficacy of the AED. AED administration, including the time of dosing and dose frequency, may be adjusted to maximize compliance and minimize adverse effects. AEDs that have gastric side effects such as ethosuximide and valproate may be better tolerated if taken with meals. Patients adhere to once- or twice-daily dosing regimens more easily than to regimens requiring three or more daily doses. Dosing frequency is directly related to half-life; the longer the half-life, the longer the interval between doses.[36]

In well-controlled adult patients, most clinicians would monitor AED serum levels once or twice per year. Serum levels are meaningful only if measured during steady-state conditions. Normally, steady-state serum levels are reached after five half-lives have elapsed; thus, time to steady-state levels after start of AED therapy varies for each AED. Pediatric patients often require more frequent serum level monitoring because AED metabolism is affected by developmental changes, including growth spurts and the onset of puberty.[36]

AEDs: General Discussion

For most of the 20th century, approximately 50% of patients with epilepsy who were treated with the traditional AEDs achieved partial or complete freedom from seizures. This has represented a major achievement; however, treatment with the traditional AEDs has some shortcomings; some patients continue to sustain seizures and/or experience severe adverse events. The traditional AEDs are considered to be those approved for use before 1990 and include phenobarbital, phenytoin, primidone, carbamazepine, and valproate.

Eight new AEDs have been introduced since 1993 (Table 9), and more are expected to be approved by the Food and Drug Administration (FDA) in the future. Most of the data about the new AEDs comes from adjunctive trials that generally followed a uniform design. The patients enrolled had refractory partial epilepsy despite AED treatment. After an initial baseline evaluation of 8 to 12 weeks, patients were randomized to receive either the new study AED or placebo; all patients continued to take their original AED. The double-blind phase was typically 8 to 12 weeks, and the main efficacy outcome measure was reduction of seizure frequency over baseline compared with placebo.[37]

Table 9
AEDs APPROVED FROM 1993 THROUGH 2000

• Felbamate	• Tiagabine
• Gabapentin	• Levetiracetam
• Lamotrigine	• Zonisamide
• Topiramate	• Oxcarbazepine

An important benefit of this type of trial design is that patients can be enrolled with the assurance that, regardless of which study group they are randomized to, they will continue to receive baseline doses of their original AED.[37] However, the drawbacks of this type of trial are considerable. It is difficult, if not impossible, to determine if an adverse effect is due to the add-on AED, to an interaction between the original AED and the add-on AED, or to the original AED. Many of the traditional AEDs are either inducers or inhibitors of the P450 hepatic cytochromes (CY). If the add-on AED is metabolized by the same route, the interaction between the two AEDs could either lower (in the case of inducers) or raise (in the case of inhibitors) the drug level of the newer AED, affecting both efficacy and adverse events.[37] The same effect could take place in reverse; that is, the new AED could raise or lower serum levels of the baseline drug. This, however, is less likely since the new AEDs interact with CYP450 enzymes less often than the older AEDs.

Adjunctive trials in patients with refractory epilepsy are not comparable to how the new AEDs would be used in clinical practice. The study patients are much more difficult to treat than most patients with seizures. As stated earlier, the response rates to subsequent AEDs in patients who have failed AED therapy because of inadequate seizure control are quite low. In addition, these trials cannot address the question of how well an AED can be expected to work as monotherapy in patients with newly diagnosed epilepsies.

Adjunctive trials have demonstrated efficacy for topiramate, felbamate, gabapentin, lamotrigine, levetiracetam, tiagabine, oxcarbazepine, and zonisamide. These AEDs were approved for adjunctive use in patients whose seizures are inadequately controlled. Placebo-controlled crossover trials also have been conducted, and some of the new AEDs have been compared directly with traditional AEDs. Meta-analyses have been done in which clinical trial results were compared as odds ratios for 50% seizure reduction compared with baseline. These studies included some trials in which new AEDs were given at a very high or very low dose, thus either overstating or understating both efficacy and adverse-event profiles.

Clinical trials comparing new AEDs as monotherapy, at currently accepted therapeutic doses, in matched patient populations would allow optimal comparison among these agents.[38] To date, randomized controlled trials comparing AEDs as initial monotherapy have been limited to patient populations with a specific seizure type (ie, partial-onset or GTC seizures). Recent comparative studies have been limited to two treatment arms comparing a newer AED with a traditional AED such as carbamazepine. A unique double-blind study was recently designed to minimize these limitations so that results could be generalized to patients with newly diagnosed epilepsy.[39] This study compared topiramate with either carbamazepine or valproate (depending on patients' seizure types and profiles) as initial monotherapy in newly diagnosed epilepsy. No seizure type or epilepsy syndrome was excluded. Investigators chose whether they would have treated the individual patient with carbamazepine or valproate. Then, the patient was randomized to either the investigator's choice, topiramate 100 mg/d, or topiramate 200 mg/d, as monotherapy.

Study results demonstrated that topiramate is useful as first-line therapy in patients with newly diagnosed epilepsy. In newly diagnosed epilepsy, topiramate (100 or 200 mg/d) was shown to be as effective and well tolerated as carbamazepine (600 mg/d) or valproate (1250 mg/d). Furthermore, qualitative differences in side-effect profiles allow AED monotherapy to be tailored to an individual patient.

Most experts agree that monotherapy use of new AEDs that have proven safety and efficacy as adjunctive therapy is often justified (Table 10). Valuable conclusions may be drawn from the studies that have been carried out (Table 11). Severe adverse events that may occur with traditional AEDs generally do not happen with the newer AEDs. Exceptions to this are cases of aplastic anemia that have been associated with felbamate, Stevens-Johnson syndrome with lamotrigine, and hypersensitivity with zonisamide. The newer AEDs have minimal interactions with the CYP450 metabolic pathway. Thus, they are less likely to provoke drug-drug interactions, with either other AEDs or other concomitant therapies, although both oxcarbazepine and topiramate may induce hepatic metabolism and reduce the efficacy of oral contraceptives (OCs).

Gabapentin is widely approved as add-on therapy for epilepsy treatment for partial seizures with and without secondary generalization.[40] To investigate the efficacy of gabapentin administered as monotherapy, three large multicenter, double-blind, parallel-group, dose-controlled trials were performed.[37] In the first trial, 275 outpatients with refractory partial epilepsy maintained on stable doses of one or two AEDs were switched to gabapentin monotherapy at 600 mg, 1200 mg, or 2400 mg daily. Patients were required to exit the trial if they experienced worsening of seizure frequency. In the second study, 82 hospitalized patients with medically refractory epilepsy were tapered off baseline AEDs and randomly assigned to gabapentin monotherapy at 300 or 3600 mg/d; in the third trial, 292 patients with newly diagnosed partial seizures were randomized to gabapentin 300, 900, or 1800 mg/d or to carbamazepine 600 mg/d. Patients remained in the second trial 8 days but had to exit if they experienced one or more exit events; in the third study, patients remained in the trial for up to 6 months or until they experienced an exit event.

With respect to time to exit, there were no statistically significant differences among the three groups. Patients who withdrew from the first and second studies due to adverse events were 3% and 0%, respectively. Patients who received carbamazepine had a higher withdrawal rate due to adverse events compared with the gabapentin 900- and 1800-mg/d groups. Mean time to exit for patients who received gabapentin 900 mg/d (P=0.02) or 1800 mg/d (P=0.04) was significantly longer versus carbamazepine. Completion rates for carbamazepine were similar to both gabapentin 900- and 1800-mg/d groups.[37] In summary,

Table 10

EFFICACY OF MONOTHERAPY WITH NOVEL AEDs IN ADULTS: RESULTS OF RANDOMIZED CLINICAL TRIALS*

	Refractory Partial Seizures	Newly Diagnosed Partial Epilepsy	Newly Diagnosed Partial or Generalized Epilepsy	Absence Seizures
Felbamate	✓			
Gabapentin	✓	✓		
Lamotrigine	✓		✓	✓
Topiramate	✓	✓	✓	
Tiagabine	✓			
Levetiracetam	✓			
Zonisamide	✓			
Oxcarbazepine	✓		✓	

*May refer to nonapproved indications.

Adapted with permission from Brodie MJ, Pellock JM. *Lancet.* 1995;346:918-919. Beydoun A. *Epilepsia.* 1997;38(suppl 9):S21-S31.

Table 11

ADVANTAGES OF NEWER AEDs OVER TRADITIONAL AEDs*

- Reduced occurrence of severe adverse events
- Overall improved tolerability
- Minimal or no interaction with CYP450 metabolic pathway
- Decreased incidence of drug-drug interactions
- Broader spectrum of activity

*Advantages as a group; factors may vary among individual AEDs.

there is good evidence that gabapentin at 900 or 1800 mg/d is efficacious and safe as monotherapy for the treatment of partial-onset seizures.[37,40]

Use of lamotrigine as monotherapy was investigated in a double-blind, randomized, parallel-group comparison with carbamazepine in newly diagnosed epilepsy.[41] Of 260 patients (131 lamotrigine, 129 carbamazepine) in eight UK centers, 151 completed the 48-week trial. There were no differences in efficacy for partial seizures with or without secondary generalization or for primary GTC seizures between the drugs. The proportion of patients maintained seizure-free during the last 24 weeks of treatment was almost the same (39% for lamotrigine, 38% for carbamazepine). However, fewer patients on lamotrigine than on carbamazepine withdrew because of adverse events (15% vs 27%). The most common side effect was rash (9% vs 13%). More lamotrigine than carbamazepine recipients (65% vs 15%; *P*=0.018) completed the study (hazard ratio 1.57 [95% CI 1.07 to 2.31]). In conclusion, lamotrigine and carbamazepine showed similar efficacy against partial-onset seizures and primary GTC seizures in newly diagnosed epilepsy; however, lamotrigine was better tolerated.[41]

The safety and efficacy of oxcarbazepine monotherapy were evaluated in four international trials in patients with newly diagnosed partial-onset or GTC seizures. Oxcarbazepine was compared with phenytoin in two of the trials in 287 patients aged 16 to 65 years. In both trials, phenytoin and oxcarbazepine had similar efficacy with 58% to 60% of patients remaining seizure-free during the maintenance phase; however, oxcarbazepine was tolerated significantly better than phenytoin in both trials. The withdrawal rates due to adverse events were 2% to 4% for patients treated with oxcarbazepine and 11% to 15% for patients randomized to phenytoin. The third trial compared oxcarbazepine with valproate, and no significant differences were demonstrated in seizure-free patients or tolerability between treatment groups. Although no significant differences in efficacy were observed between oxcarbazepine and carbamazepine in the fourth clinical trial, oxcarbazepine was tolerated significantly better (14% for oxcarbazepine and 26% for carbamazepine).

Table 12
NEWER AEDs AND SPECTRUM OF ACTIVITY

	Partial	Lennox-Gastaut	Juvenile Myoclonic Epilepsy	Absence	Generalized Tonic-Clonic Seizures
Zonisamide	+	?+	?+	?+	?
Gabapentin	+	-	-	-	?
Lamotrigine	+	+	?+	?+	?
Topiramate	+	+	?+	?	+
Levetiracetam	+	?	?+	?+	?
Tiagabine	+	-	-	-	?
Oxcarbazepine	+	-	-	-	?
Felbamate	+	+	?	?	?

+ = randomized controlled trials;?+ = case reports or open-label trials only; ? = no data; - = any negative data or evidence of worsening.

In conclusion, the newer AEDs offer a broader spectrum of efficacy (partial- and generalized-onset seizures) in comparison to the traditional AEDs. Randomized controlled trials have demonstrated broad-spectrum efficacy for felbamate, lamotrigine, and topiramate. A broad spectrum of efficacy may minimize both the need for frequent switching of AED therapies and side effects (Table 12).

AED Safety and Adverse Effects

In order to make informed therapeutic decisions, clinicians need to combine information from clinical trials with other data, including knowledge of the AEDs, mechanism(s) of action, potential for drug-drug interactions, and potential use in various patient populations. The choice of pharmacologic treatment requires consideration of the diagnosis and severity of adverse effects. Because epilepsy is often chronic, AEDs will be taken for years, and adverse events may occur as a result of long-term therapy.

Classification of Adverse Effects

Several classifications of adverse events may be used. Regulatory agencies such as the FDA attempt to classify adverse events as to severity, eg, serious, life-threatening, and unexpected. A further classification is according to organ system: cardiovascular, gastrointestinal, hepatic, hematologic, and lymphatic. Classifying adverse events of AEDs in terms of their mechanisms of action is essential; however, the mechanisms of most adverse effects are not thoroughly understood and cannot yet be classified in this manner.[42]

A distinction between dose-related and idiosyncratic effects links the adverse effect to the AED causing it. Dose-related effects are those that would be expected to affect many or most individuals, with a higher percentage of individuals being affected as the dose increases and with adverse effects diminishing with dose reductions. Dose-related side effects arise directly from the pharmacologic effects of the drug and are relatively host-independent. Idiosyncratic effects are those that occur rarely, are not clearly dose-related, are host-dependent, and can be serious and even life-threatening.[42,43] Furthermore, some side effects are cumulative after long-term therapy, such as dependence after long-term barbiturate use, carcinogenicity, or peripheral neuropathy.[43]

Idiosyncratic reactions are associated with both the traditional and the newer AEDs (Tables 13 and 14). Overall, idiosyncratic drug reactions occur in less than 0.1% of the general population, but they account for approximately 10% of all drug reactions. The typical incidence of an idiosyncratic drug reaction is from 1 in 100 exposures to 1 in 100,000 exposures. Because the incidence is so low, idiosyncratic drug reactions rarely are detected in clinical trials and become known only after the drug is in wide use.[43]

Currently, research is under way to develop methods of identifying persons who are likely to experience idiosyncratic drug reactions. These include development of "at-risk" profiles for a particular AED, identification of biomarkers that measure the formation of a toxic metabolite for a particular AED, identification of biomarkers indicating deficient detoxification abilities for a host, and development of "at-risk" genetic markers.[43] At-risk clinical profiles have been developed for some specific AEDs such a valproic acid, felbamate, and lamotrigine (Table 15, page 18), and they are useful in identifying patients at risk for developing idiosyncratic reactions.

Table 13
IDIOSYNCRATIC REACTIONS ASSOCIATED WITH TRADITIONAL ANTIEPILEPTIC MEDICATIONS

Reaction	CBZ	ESM	PB	PHT	VPA
Agranulocytosis	✓	✓	✓	✓	✓
Stevens-Johnson syndrome	✓	✓	✓	✓	✓
Aplastic anemia	✓	✓		✓	✓
Hepatic failure	✓		✓	✓	✓
Allergic dermatitis/rash	✓	✓	✓	✓	✓
Serum sickness reaction	✓	✓	✓	✓	✓
Pancreatitis	✓			✓	✓

CBZ, carbamazepine; ESM, ethosuximide; PB, Phenobarbital; PHT, phenytoin; VPA, valproic acid.

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Exacerbation of Seizures by AEDs

Instead of reducing the frequency and severity of seizures, there are instances when AEDs have done the opposite (Table 16, page 19). A number of mechanisms have been postulated that may lead to paradoxical worsening of the patient's condition, including use of an AED that is not appropriate for the seizure type, noncompliance, repeated withdrawal, overdosage, acute idiosyncratic effects, chronic dose-related effects, and others. The principal culprit, however, is the inverse pharmacodynamic effect.[44-46]

Most of the AEDs can cause seizure worsening at high doses (eg, in toxic overdoses), but phenytoin can exacerbate seizures at supratherapeutic levels (usually ≥30 mg/mL) that can be achieved with modest increase in doses.[46]

Idiopathic generalized epilepsies are particularly susceptible to exacerbation by certain AEDs. Absence seizures may be increased by carbamazepine, vigabatrin, and tiagabine; phenytoin is less aggravating, and phenobarbital may decrease absence seizures at low doses and increase them at higher doses. Myoclonus and absence seizures in patients with JME are often exacerbated by carbamazepine. GTC seizures may respond to AEDs that intensify the other idiopathic generalized epilepsies; thus, withdrawal of carbamazepine in a patient whose absence seizures have worsened should be performed gradually.[44]

Because of the propensity to exacerbate seizures, carbamazepine is contraindicated in patients with absence epilepsy, infantile myoclonus, or JME. Caution should be used in patients with mixed seizure disorders.[46]

Table 14
IDIOSYNCRATIC REACTIONS ASSOCIATED WITH NEWER ANTIEPILEPTIC MEDICATIONS

	Felbamate	Gabapentin	Lamotrigine	Topiramate	Tiagabine	Oxcarbazepine	Zonisamide
Agranulocytosis	X						
Stevens-Johnson syndrome			X				X
Aplastic anemia	X						
Hepatic failure	X						
Allergic dermatitis/rash	X	X	X	X	X	X	X

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The Newer AEDs

Until the 1990s, five agents—phenobarbital, phenytoin, primidone, carbamazepine, and valproate—constituted the principal armamentarium in the management of epilepsy, with ethosuximide being used for absence seizures only. During the 1990s, eight more AEDs were developed and approved for use: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, zonisamide, tiagabine, and topiramate. At least six more AEDs are currently under development, and some of these will become available over the next 10 years.

Table 15

CLINICAL PROFILE FOR PATIENTS AT HIGH RISK FOR IDIOSYNCRATIC REACTIONS TO VALPROIC ACID, FELBAMATE, AND LAMOTRIGINE

Valproic Acid (Hepatotoxicity)	Felbamate (Aplastic anemia)	Lamotrigine (Stevens-Johnson syndrome or toxic epidermal necrolysis)
Children under the age of 2 years	Caucasian	Children more than adults
Multiple concomitant AEDs	Adults more than children	Concurrent valproic acid use
Underlying metabolic disease	Females more than males	High starting dose
Developmental delay	Previous cytopenia	Rapid titration
	History of an AED allergy or toxicity	On lamotrigine less than 1 year
	History of an immune disorder	
	On felbamate less than 1 year	

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At present, carbamazepine is likely to be the first drug used in patients with partial-onset seizures, while valproate is usually the first choice for generalized-onset seizures. The choices are based on extensive experience with these AEDs, which includes their efficacy profiles and the risk for adverse events. In many cases, the clinician will employ one of the newer AEDs as either adjunctive therapy, when the first AED does not provide adequate seizure control, or as monotherapy after failure of one or more traditional AEDs. Randomized controlled trials have directly compared several of the newer AEDs with carbamazepine. The newer AEDs were equivalent in efficacy, and in some cases better tolerated, than carbamazepine. In some instances, clinicians may choose one of the newer AEDs as monotherapy for new-onset cases.

The efficacy profiles of the eight new AEDs are shown in Figure 4 (page 20). The data are from a series of adjunctive studies, together with trials designed for regulatory approval. The patients enrolled in these trials had complex partial epilepsy, with four or more seizures monthly. The efficacy outcome was stated as the odds ratio for a 50% reduction in seizures compared with the baseline period.[47] The odds ratios for response are shown on the vertical axis, and these run from approximately 1.93 for vagus nerve stimulation (VNS) to just over 4.0 for topiramate. The odds ratios for withdrawal are shown on the horizontal axis; these run from approximately 1.08 for VNS to approximately 2.5 for topiramate.[47] Withdrawal could be for any reason, including the patient's inability to tolerate adverse effects or lack of compliance.

The black line running diagonally divides the AEDs into two groups. Above and to the left of the black line are the AEDs whose odds ratios for response outweigh their odds ratios for withdrawal—topiramate, levetiracetam, tiagabine, and lamotrigine. Below and to the right are the AEDs whose odds ratios for withdrawal outweigh their odds ratios for response—oxcarbazepine, gabapentin, zonisamide, and VNS. VNS has recently been introduced as an adjunct for treating patients with drug-resistant partial seizures and appears to be an effective and well-tolerated treatment. Adverse effects of hoarseness, cough, pain, paresthesia, and dyspnea are associated with the treatment but appear to be reasonably well tolerated, as dropouts were rare. Typical CNS adverse effects of AEDs such as ataxia, dizziness, fatigue, nausea, and somnolence were not statistically significantly associated with VNS treatment.[48,49] VNS, a new nonpharmacologic treatment, is a reasonable option in patients in whom AED treatment has failed.[50]

Comparative analysis of the adjunctive studies yields further insight into the efficacy profiles of the newer AEDs. Because the outcome criterion is percentage of improvement versus placebo, the placebo success rates become highly important. In these studies, the placebo success rates ranged from a low of 4% to 6% for tiagabine to a high of 5% to 18% for topiramate. The relatively high odds ratio for success attributed to tiagabine (3.5 to 3.7) is in part due to the low placebo success rate.[38] While these meta-analyses and comparisons are far from definitive, they may be useful to clinicians in selecting the appropriate AEDs for their patients.

Felbamate

Felbamate was the first of the newer AEDs to be introduced, approved for use in the United States in 1993, with indications for monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without generalization in adults, or as adjunctive therapy in the treatment of partial-onset and generalized-onset seizures associated with the Lennox-Gastaut syndrome in children, and it appears to be safer in the pediatric population.[51] However, within 1 year after the introduction of felbamate in the United States, there were reports of aplastic anemia in adult patients, primarily women (34 cases by 1999), and 18 cases of liver failure, some fatal. In August 1994, the FDA sent out a "Dear Doctor" letter, advising clinicians to discontinue therapy in all patients except those who would suffer substantially from its withdrawal. Nevertheless, more than 10,000 patients worldwide continue to receive felbamate, most of whom have failed to achieve satisfactory seizure control with several other AEDs.[52,53]

Gabapentin

Gabapentin was the second of the newer AEDs to be introduced. It is indicated as adjunctive therapy for partial-onset seizures with and without secondary generalization in adults with epilepsy. Gabapentin increases GABA levels in the brain; increasing the relative proportion of GABA to glutamate may lead to subtle inhibition and reduced excitotoxic damage. Gabapentin also may have some effect on the voltage-gated Ca++ channel.[54,55]

Several Phase III adjunctive clinical trials demonstrated differences between 50% response rates for gabapentin versus placebo, eg, gabapentin – 23%, placebo – 9%; gabapentin – 16%, placebo – 8%; and gabapentin – 22%, placebo – 10%.[54] However, a more recent open-label trial (the Study of Titration to Effect Profile of Safety [STEPS] trial) in 1055 patients reported much more robust response rates for gabapentin. The average decrease in seizure frequency in this group was 61%; 46% were seizure-free during the last 4 weeks of the study; 76% were judged to be responders. The STEPS trial differed from the earlier trials in that gabapentin doses were increased to up to 3600 mg/d. The patients enrolled in this trial, although diagnosed with partial epilepsy resistant to treatment with other AEDs, were probably not as refractory as those in the Phase III trials.[56] Open-label trials of AEDs typically show higher response rates, and these results are difficult to compare directly to randomized controlled trials.

Gabapentin is not metabolized in humans, does not bind to plasma proteins, and does not induce or inhibit hepatic enzymes. Thus, the likelihood of drug-drug interactions is small, and such interactions have not been observed.[55]

The adverse events associated with higher doses that occurred most frequently in adjunctive trials of gabapentin were somnolence, dizziness, ataxia, fatigue, and nystagmus. Most clinicians do not use gabapentin extensively in patients who have failed trials of other AEDs because of a perception of modest efficacy for gabapentin. Currently gabapentin is prescribed more frequently for neuropathic pain and bipolar disorders (off-label uses). For the five adverse events listed above, the percentage of patients taking gabapentin plus the baseline anticonvulsant experiencing the adverse event was higher than the percentage taking placebo plus the baseline anticonvulsant; thus, it may be reasonable to conclude that the cause of this difference was the adjunctive drug.[57]

Three million patients have been treated with gabapentin through 1998 without an established causal relationship to a specific life-threatening organ toxicity. Relatively few patients experience intolerable side effects, even at high doses. In general, the doses used in clinical trials were ≤50% than the maximal doses used by physicians who claim greatest success. Suggested dose ranges are from 900 to 1200 mg/d in new-onset cases, and from 2400 to 4800 mg/d for patients who have failed three or more AEDs before a gabapentin trial.[55]

There have been reports that gabapentin has been associated with exacerbation of seizures. Fifteen percent of 263 patients in a tertiary epilepsy referral center experienced seizure worsening while being treated with gabapentin. Gabapentin also has been reported to cause seizure worsening in up to 15% of patients with learning disabilities.[57] In a randomized controlled trial, gabapentin was ineffective in controlling absence or myoclonic seizures.[40]

Table 16
AEDs AND WORSENING OF SEIZURES

- Drug intoxication–nonspecific
  - Reduce dose
  - Eliminate polypharmacy
- Drug-specific increase in seizure types
  - Carbamazepine — absence, atonic, myoclonic (generalized)
  - Phenobarbital — negative myoclonus, tonic, absence
  - Phenytoin — absence, atonic, myoclonic
  - Ethosuximide — tonic-clonic (?)
  - Gabapentin/lamotrigine — myoclonic
  - Benzodiazepine (IV) — tonic
  - Tiagabine — myoclonic, nonconvulsive status epilepticus (?)
  - Oxcarbazepine — similar to carbamazepine
  - Levetiracetam — change in seizure types (?)

Zonisamide

Zonisamide, an active antiseizure drug with a unique mechanism of action, was approved by the FDA in March 2000 as adjunctive therapy in adults with partial-onset seizures. Three multicenter, placebo-controlled, double-blind studies examined the effects of zonisamide as an adjunctive therapy in 499 patients with refractory partial-onset seizures with or without secondary generalization. In one study, there was a 40.5% mean reduction in partial-onset seizures for those on placebo. In the other two studies, partial-onset seizures were reduced by a mean of 27% to 30% in those treated with zonisamide, compared with slight increases in frequency in those on placebo.[58] Open-label studies from Japan, where zonisamide has been approved for more than 10 years, suggest the drug may be effective in generalized-onset seizures.[59]

The major adverse effects associated with zonisamide are drowsiness (24%), ataxia (13%), loss of appetite (11%), gastrointestinal problems (7%), and slowing of mental activity (5%).[57] In addition, about 1% to 2% of treated patients develop kidney stones, and the risk is apparently greater in those with a family history.[58] Zonisamide is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides. Furthermore, there is a warning for potentially fatal reactions (although rare) as a result of severe reactions to sulfonamides, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias.

Lamotrigine

Lamotrigine is indicated for adjunctive therapy in adults with partial-onset seizures and as adjunctive therapy in the generalized-onset seizures of Lennox-Gastaut syndrome in adult and pediatric patients.[54] In the United Kingdom, it is licensed as monotherapy for partial-onset seizures with or without secondarily GTC seizures in patients older than 12 years and as adjunctive therapy for children older than 2 years. The mechanism of action of lamotrigine is thought to be inhibition of the sodium channel as well as inhibition of glutamate release.[57]

In adjunctive trials similar to those described earlier, lamotrigine's effectiveness in achieving 50% seizure reduction was linked to dosing levels. At 300 mg/d, the percentage of patients achieving 50% seizure reduction was 17% for lamotrigine versus 14% for placebo; the rate improved to 34% for lamotrigine versus 18% for placebo when the dosage was increased to 500 mg/d. In a crossover trial, the improvement rates were 19% for lamotrigine versus 6% for placebo.[38]

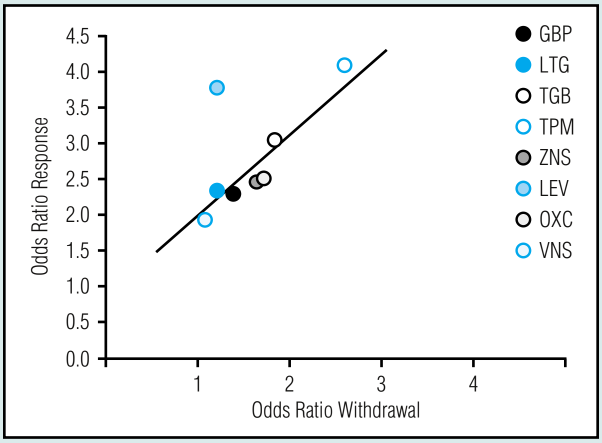
Lamotrigine also has been compared directly with the two traditional AEDs, carbamazepine and phenytoin. Both trials were in newly diagnosed patients older than 13 years; in neither trial were there statistically significant differences between the drugs.[53,60] Lamotrigine and valproate were compared in a trial enrolling medically refractory patients 13 years of age or older. Patients had sustained eight or more partial-onset seizures while on maintenance therapy with either phenytoin or carbamazepine. An important outcome measure was time to treatment failure, defined in terms of seizure frequency or severity. The percentage of treatment failures in the lamotrigine group was 63%, compared with 84% in patients treated with valproate. Median time to treatment failure was significantly longer in lamotrigine-treated than in valproate-treated patients, 80 days versus 58 days (P=0.027).[61]

Lamotrigine also was studied in a small trial involving children and adolescents with typical absence seizures. The primary efficacy variable was the proportion of patients who remained seizure-free during the 20-week double-blind phase. Of the 28 patients in the double-blind phase, 64% remained seizure-free, compared with 36% of placebo-treated patients (P<0.05).[62]

The most common adverse events reported in the adjunctive trials were dizziness, somnolence, headache, diplopia, ataxia, blurred vision, and nausea. In a side-by-side study of lamotrigine and carbamazepine, the only adverse event for which there was a statistical difference between the two groups was somnolence, which affected 22% of carbamazepine-treated patients versus 12% of lamotrigine-treated patients.[57]

The adverse event most often leading to discontinuation of lamotrigine therapy is skin rash, which occurs in 5% to 10% of patients. In most cases, the rash is a simple morbilliform rash without evidence of systemic involvement. Coadministration of lamotrigine and valproate and use of a high starting dosage and rapid dosage increases are risk factors for lamotrigine-associated rash.[57]

Figure 4
ODDS RATIO OF RESPONSE VERSUS WITHDRAWAL



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Stevens-Johnson syndrome associated with lamotrigine use has been reported in clinical trials, with an incidence of approximately 1 in 1000 patients. This adverse event, a somewhat less severe form of toxic epidermal necrolysis (which also has been reported, although rarely), requires discontinuation of treatment and hospitalization. Multi-organ, hepatic, and renal failure, as well as leukopenia, also have been reported.[57] Lamotrigine rash appears to be more common children.[63]

Levetiracetam

Levetiracetam was approved for use in the United States in December 1999. It is indicated as adjunctive treatment for partial-onset seizures in patients 16 years of age or older.[64] The mechanism of action of levetiracetam has not been fully elucidated; however, several potential excitatory foci have been ruled out. Levetiracetam does not appear to interact with either inhibitory or excitatory neurotransmission, nor does this AED affect membrane excitability. Recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability.[44]

Levetiracetam has been evaluated in several clinical trials, including both double-blind, placebo-controlled studies and open-label studies. Overall, levetiracetam was more effective than placebo in achieving median weekly reductions in seizure frequency and in percent of patients demonstrating a 50% response rate. In a study of 286 patients, those taking 1000 mg/d levetiracetam had 20.9% weekly reductions in seizure frequency, and 33% of these patients had a 50% response rate. For those patients taking 2000 mg/d levetiracetam, the comparable figures were 27.7% and 39.8%, respectively; placebo-treated patients had a 6.8% reduction in seizure frequency and 10.8% had a 50% response rate. Another study in patients with partial epilepsy showed comparable results. These patients had epilepsy for at least 2 years and had sustained at least 12 seizures in the 12 weeks prior to enrollment. Of the 294 patients assigned to treatment groups, 268 completed the study. Patients (n=98) taking 1000 mg/d levetiracetam had 20.9% weekly reductions in seizure frequency, and 33% of these patients had a 50% response rate. For those patients (n=101) taking 3000 mg/d levetiracetam, the comparable figures were 27.7% and 39.8%, respectively; placebo-treated patients (n=95) had a 6.8% reduction in seizure frequency and 10.8% had a 50% response rate.[65]

A double-blind adjunctive study compared 1000 and 2000 mg/d levetiracetam with placebo in patients (n=324) with refractory epilepsy who had failed treatment with at least two AEDs. Both dosages of levetiracetam significantly decreased seizure frequency compared with placebo (1000 mg/d, 16.4%; 2000 mg/d, 17.7%); however, the differences between the two dosages were not significant.[66]

The most common adverse effects reported with levetiracetam have been somnolence, irritability, asthenia, and dizziness. These effects are more commonly seen in patients started at doses of 1000 mg/d and are more prevalent at higher doses.[64]

Levetiracetam's pharmacokinetic profile suggests that interactions with other drugs are unlikely. Protein binding is clinically insignificant, and the drug is neither an inducer nor an inhibitor of hepatic CYP isoforms. The addition of levetiracetam to phenytoin resulted in significant elevations of phenytoin concentrations (27% to 52%) in rare instances. The half-life of levetiracetam is approximately 7 hours, resulting in steady-state concentration after 2 days of therapy.[64]

Some meta-analyses suggest that the efficacy and tolerability of levetiracetam are comparable to those of existing AED treatments; however, no trial data exist comparing levetiracetam directly with other AEDs.[64]

Oxcarbazepine

Oxcarbazepine has been registered in more than 50 countries since 1990, and it has recently been approved in the United States for the treatment of partial-onset seizures as monotherapy or adjunctive therapy in adults and as adjunctive therapy in children. Oxcarbazepine is a 10-keto analogue of carbamazepine. It undergoes rapid and almost complete metabolism of its keto group to form the active 10-monohydroxy derivative (MHD).[67] The efficacy of oxcarbazepine is similar to that of carbamazepine, but the newer AED has fewer adverse effects and drug interactions.[57]

Oxcarbazepine has been evaluated in 10 large controlled trials, including placebo-controlled trials, substitution-dose-controlled trials, and comparative trials. In a placebo-controlled trial whose primary efficacy variable was time to first seizure after randomization, oxcarbazepine performed significantly better than placebo. Time to first seizure was 11.7 days for patients in the oxcarbazepine group versus 3.2 days for the placebo group (P=0.0457).[67]

Three comparative monotherapy trials have been conducted evaluating oxcarbazepine with valproic acid (one study) and with phenytoin (one study in children and one in adults). Patients in these studies had had two or more partial-onset seizures in the preceding 6 months and had received no AED therapy. In all three trials, oxcarbazepine, valproic acid, and phenytoin demonstrated similar efficacy. There was no difference between oxcarbazepine- and valproic acid-treated patients with regard to seizure freedom during the 48-week maintenance period. Fifty-seven percent of oxcarbazepine-treated patients were seizure-free compared with 54% of those treated with valproic acid. Similar results were seen in the oxcarbazepine-phenytoin trial, where the seizure-free percentages were 59% for oxcarbazepine and

58% for phenytoin. In children, the results were 61% seizure-free in the oxcarbazepine group and 60% seizure-free in the phenytoin group.[67]

In a fourth trial, oxcarbazepine was compared with carbamazepine in patients with newly diagnosed and previously untreated epilepsy with either partial-onset seizures (with or without secondarily generalized-onset seizures) or GTC seizures. There was no significant difference between seizure freedom in the oxcarbazepine group (52%) and the carbamazepine group (60%).[67]

The most common adverse events associated with oxcarbazepine treatment are fatigue/weakness, headache, dizziness, somnolence, ataxia, nausea, vomiting, and diplopia. Each of these events, with the exception of headache, was observed more frequently in patients receiving oxcarbazepine in adjunctive therapy than as monotherapy.[67] Hyponatremia appears to be common with oxcarbazepine and may rarely lead to serious complications.[57] The incidence of skin rash is lower in patients treated with oxcarbazepine than in those treated with carbamazepine. In a retrospective study of 947 oxcarbazepine-treated patients, rash was reported in 6%; of these, half had developed rashes while receiving carbamazepine. About 25% of patients who have skin problems with carbamazepine may exhibit cross-reactivity with oxcarbazepine.[57]

Oxcarbazepine and the MHD metabolite are competitive inhibitors of hepatic CYP450 isoenzyme 2C19, an enzyme involved in the metabolism of phenytoin. When other AEDs that employ the same metabolic pathways are used with oxcarbazepine, serum concentrations of oxcarbazepine, MHD, or the other AED may be increased or decreased, requiring dosage adjustment and potentially leading to adverse effects. The AEDs with which oxcarbazepine has been demonstrated to interact include phenytoin, phenobarbital, and carbamazepine. No clinically significant interactions have been reported with oxcarbazepine and valproic acid.[67]

Oxcarbazepine may decrease the effectiveness of OCs by accelerating the metabolism of ethinyl estradiol and levonorgestrel through hepatic cytochromes of the CYP3A subgroup. Therefore, the concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives less effective. Studies with other hormonal contraceptive methods have not been conducted.[54,67]

Tiagabine

Tiagabine, a specific GABA reuptake inhibitor, is indicated for the adjunctive treatment of partial-onset seizures in adults and children over 12 years of age.[54]

Tiagabine appears to be moderately efficacious. At doses of 16 mg/d, 30 to 32 mg/d, and 56 mg/d, the proportion of patients who reached the 50% seizure-reduction mark were 10%, 22%, and 30%, respectively; the comparable placebo percentages were 4%, 6%, and 4%. Overall, only 21% of tiagabine-treated patients in these trials attained the 50% success rate.[38]

Most adverse events resulting from tiagabine treatment are CNS-related, occur within the first 6 months of therapy, and resolve within 1 month. The most common adverse events noted are dizziness, asthenia, nervousness, tremor, diarrhea, decreased muscle control, depression, and emotional lability.[57]

The adverse event of greatest concern in relation to tiagabine is nonconvulsive status epilepticus (NCSE), which has been reported in nine patients. All nine patients recovered following tiagabine withdrawal, which suggests that tiagabine was the cause.[57] Specific case reports of tiagabine-induced NCSE[68] and tiagabine-induced absence status in generalized epilepsy[69] suggest that tiagabine should be used cautiously in the treatment of generalized epilepsies.

Topiramate

Topiramate was approved as adjunctive therapy for the treatment of partial-onset seizures in adults in 1996. More recently, it has been approved as adjunctive therapy in adults and pediatric patients (aged 2 to 16 years) with partial-onset seizures or primary GTC seizures and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome.[54,70,71]

Topiramate has the broadest mechanism-of-action profile among newer AEDs. There is evidence that topiramate blocks voltage-gated Na+ channels, as do several other AEDs; however, Na+ channel blockade is probably not topiramate's principal mechanism of action. Topiramate also enhances GABA-mediated transmission at the $GABA_A$ receptors. This modulatory effect is different from that of the benzodiazepines or the barbiturates. Topiramate also inhibits glutamate receptors through a negative modulatory effect on kainate-evoked currents. Finally, there is some indication that topiramate selectively inhibits L-type high-voltage-activated Ca++ channels.[72]

Topiramate has demonstrated statistically significant efficacy in numerous clinical trials, and it appears to be the most potent overall of the newer AEDs.[71] As with the other newer AEDs, topiramate was first studied as adjunctive therapy in adult patients with refractory partial-onset seizures. In five trials, the proportion of patients taking topiramate 400 mg/d whose seizure frequency was reduced by 50%— ie, 50% responders—was 35% to 47%, compared with 0% to 18% for those taking placebo.[71]

Another recent study was conducted to evaluate a lower target dose—200 mg/d topiramate—as adjunctive therapy. Patients enrolled were adults aged 18 to 65 years who had experienced ≥3 partial-onset seizures during a 4-week baseline period. Results of the study demonstrated that topiramate 200 mg/d added to an enzyme-inducing AED (carbamazepine) is an appropriate target dose in adults with treatment-resistant partial-onset seizures, and that topiramate 100 mg/d may be an effective dose in some patients. Furthermore, topiramate is well tolerated when gradually escalated to 200 mg/d, and it can produce a significant therapeutic effect within the first 2 weeks of treatment.[73]

Topiramate has been evaluated specifically in Lennox-Gastaut syndrome, which is characterized by multiple types of refractory seizures, mental retardation, and a slow, spike-wave EEG pattern. It is the third new AED approved for this indication. In a study of topiramate as adjunctive therapy for this syndrome, 28% of children had a 50% reduction in seizures, compared with 14% of those treated with placebo. In a long-term extension of the study, during which the dose of topiramate could be individually adjusted, 58% of children reached the 50% response level, and 15% of the 82 patients treated for at least 6 months were completely seizure-free. Because of the incidence of severe adverse events attributed to felbamate, the primary AEDs for Lennox-Gastaut syndrome are topiramate, lamotrigine, and valproate.[71]

Some of the patients with partial-onset seizures who were studied in the adjunctive trials developed secondarily GTC seizures during the baseline period on standard therapy. Topiramate reduced the frequency of secondarily GTC seizures by 58%, with 57% of the patients attaining 50% reduction of seizures of this type. Following this result, a study was conducted in patients who had GTC seizures from the outset, and these seizures were reduced by 57% in patients taking topiramate versus 9% for those taking placebo.[71] These study results suggest that topiramate is equally effective for convulsive seizures whether they are generalized from the onset or secondarily generalized-onset seizures.

The evidence of these and other studies indicates that topiramate is a broad-spectrum AED with efficacy to treat a wide variety of seizure types, both partial-onset and generalized-onset. The efficacy profiles of AEDs have yet to be precisely defined through side-by-side clinical trials. At this time, valproate remains the AED likely to be prescribed first when treating patients with primary generalized epilepsy. However, topiramate may be an attractive adjunctive AED with valproate, since there is minimal drug interaction between the two AEDs and the synergistic effects can result in better seizure control.[71] Lamotrigine is another AED that is widely used in generalized-onset seizures.

A recent open-label study in which adults with partial-onset seizures were receiving ≥1 AEDs demonstrated that tolerability of topiramate combined with other AEDs is improved when AED cotherapy is reduced.[74] Less than 3% of the patients reported "cognitive complaints" such as difficulty with memory, concentration, or attention; psychomotor slowing; or speech disorders. This is a substantially lower incidence than what has been observed in clinical trials that have not allowed topiramate/AED flexibility or have used more rapid titration rates. By reducing AED cotherapy, topiramate can be titrated to higher and potentially more effective dosages.

The most common adverse effects seen with topiramate are CNS-related.[57] Such related side effects also are experienced more commonly in polytherapy versus monotherapy. Psychomotor slowing may occur in some patients; however, these cognitive effects frequently disappear with continued treatment or dose titration in most affected patients.[71] Cognitive adverse effects may be described by patients as difficulty with concentration, word-finding problems, or memory difficulty. These adverse effects appear to improve with time (up to 3 months) or improve with reduction of concomitant AEDs.[71] Careful and slow titration are key to minimizing these side effects in children.

Approximately three quarters of patients in one study reported some weight loss, which the patients regarded as a benefit rather than as an adverse effect. The incidence of renal stones was 1.5% in clinical trials, about two to four times the expected incidence. Adequate fluid intake should be advised for prevention.[71]

In addition, an ocular syndrome characterized by acute myopia and secondary angle-closure glaucoma has been reported in 23 patients out of 825,000 exposures. Although rare, if a patient develops this syndrome, the primary treatment to reverse symptoms is discontinuation of therapy.[54]

Management Issues in Special Populations

Children

Most epilepsies in children are idiopathic, and about one half of children who sustain a first unprovoked seizure will not have another seizure. The recurrence rate is much higher for the relatively small percentage (11%) of children whose first seizures are complex partial-onset seizures; 79% of those patients have recurrences. There are no studies that indicate that any one AED is superior to the others for newly diagnosed partial epilepsies or for epilepsies with only GTC seizures; the only exception is phenobarbital, which should be avoided because of its cognitive adverse effects.[75] Although there are no comparative studies showing AED superiority in these seizures, there are therapeutic issues to consider.

The treatment of children with epilepsy differs from the adult patient population in several areas: AED pharmacokinetics, higher or lower risk of various adverse events, and variation of seizure type and syndromes are among the most obvious.

Because children have more rapid metabolisms than adults, most AEDs may need to be dosed somewhat higher on a milligram-per-kilogram basis. The clearance of AEDs is substantially higher in children and even higher in infants compared with adults. The clearance of a drug is a function of the elimination half-life (generally shorter in children) and the volume of distribution (larger in children). Since the clearance is equal to the ratio of the maintenance dose (mg/kg/d) divided by the average steady-state serum concentration of a drug, a higher clearance value will result in a correspondingly higher dosage requirement (mg/kg/d) for the same desired steady-state serum level. A general rule for most AEDs is that the clearance is approximately 50% higher in school-age children than in adults and >100% higher in infants.

AED toxicity is likely to be seen sooner in children than in adults and sometimes manifests as hyperactivity. AED side effects may be minimized with careful titration, starting with low doses and slowly titrating doses upwards. Several AEDs may have adverse effects that are particular to children (eg, behavioral problems, especially with phenobarbital, benzodiazepines, and gabapentin; fatal hepatotoxicity with valproate; and severe skin reactions with lamotrigine). Conversely, certain adverse effects that occur in adults have never been reported in children (eg, aplastic anemia with felbamate).

As children also have a broader spectrum of seizure types and syndromes than adults, AEDs with broad-spectrum activity are key in the treatment of pediatric epilepsy. Drugs of first choice and sequence of therapy are based on the benefit-versus-risk ratio (Table 17).

Of the newer AEDs, topiramate is indicated for adjunctive therapy in children aged 2 to 16 years with partial-onset seizures or primary GTC seizures. Recently, it was approved for use in patients 2 to 16 years of age with seizures associated with Lennox-Gastaut syndrome. Lamotrigine is indicated only for adjunctive therapy in the treatment of generalized-onset seizures associated with Lennox-Gastaut syndrome. The indication for felbamate includes adjunctive therapy for both partial-onset and generalized-onset seizures associated with Lennox-Gastaut syndrome in children. Tiagabine is indicated for adjunctive therapy for children aged 12 years and older in the treatment of partial-onset seizures. Oxcarbazepine is approved for adjunctive therapy in the treatment of partial-onset seizures in children aged 4 to 16 years. Gabapentin, levetiracetam, and zonisamide are not indicated (FDA approved) for treatment of epilepsy in the pediatric population.

Women of Childbearing Age

Women of childbearing age with epilepsy are faced with specific issues (Table 18, page 26). Women with epilepsy are more likely to experience irregular and/or abnormally long/short menstrual cycles. Approximately one third of women with epilepsy have abnormalities of ovarian function, and one third of cycles are anovulatory (compared with 10% of women without epilepsy). Studies[76] suggest that polycystic ovaries affect about 30% of women with epilepsy regardless of the AED used. However, polycystic ovaries, hyperandrogenism, hyperinsulinemia, and obesity are most likely to arise in women receiving valproate. Because of the documented reproductive problems and weight gain associated with valproate, it may be appropriate to consider using a broad-spectrum AED not associated with weight gain. AEDs such as topiramate and lamotrigine may be good options for women who demonstrate abnormalities of ovarian function as a result of epilepsy.

The use of AEDs in women of reproductive age has additional considerations regarding drug interactions. Some AEDs accelerate the metabolism of hormonal contraceptives, which may result in an unplanned pregnancy. The potential for decreased effectiveness of hormonal contraceptives, particularly those with the greatest enzyme-inducing effects such as phenytoin, phenobarbital, and carbamazepine, should be discussed. To a lesser extent, topiramate and oxcarbazepine have been shown to reduce the ethinyl estradiol component of OCs. When prescribing OCs for a patient receiving topiramate or oxcarbazepine, clinicians should consider initial therapy with an agent containing ≥35 µg ethinyl estradiol.[77]

Prepregnancy planning and counseling during pregnancy are important to women considering becoming pregnant or who have recently learned that they are pregnant.

The principal goal of treatment for women during pregnancy is maintaining optimal seizure control. Seizure frequency tends to increase during pregnancy; 23% to 46% of women sustain more seizures during pregnancy. Generalized-onset seizures are dangerous to the mother and to the fetus and can result in fetal loss and adverse neonatal and child development. Thus, in spite of the publicized risk of teratogenicity accompanying some AEDs, women should be counseled not to discontinue antiepileptic therapy or reduce doses to prevent birth defects.[78] Furthermore, teratogenesis risk increases when two AEDs are used in combination, so monotherapy is preferred whenever possible. Counseling both before pregnancy and during pregnancy is vital in women with epilepsy. Women should be reassured that most pregnancies in epileptic women are successful, especially if adequate folate supplementation is observed; 95%

Table 17
AED CHOICES IN PEDIATRIC EPILEPSY BY SEIZURE TYPE

Partial	Generalized Tonic-Clonic	Childhood Absence (<10 years)
1st choice: CBZ, OXC	1st choice: VPA, CBZ, PHT	1st choice: ESM (w/o generalized tonic-clonic or myoclonus)
2nd choice: TPM, LTG, GBP, VPA	2nd choice: TPM, LTG	2nd choice: LTG, VPA Consider: MTH, acetazolamide, BZD, ZNS, TPM
3rd choice: TGB, ZNS, PHT, LEV, PB, PRM Consider: BZD, acetazolamide, FBM	3rd choice: PB, PRM Consider: ZNS	
Childhood Absence (>10 years)	**Juvenile Myoclonic**	**Progressive Myoclonic**
1st choice: VPA monotherapy	1st choice: VPA	1st choice: VPA
2nd choice: LTG adjunctive	2nd choice: TPM, LTG, CBZ	2nd choice: ZNS, VPA + clonazepam, PB
3rd choice: ETH, MTH, acetazolamide, BZD, TPM, ZNS	3rd choice: PB, PRM, ZNS Consider: FBM	
Lennox-Gastaut and Related Syndromes	**Infantile Spasms**	**Neonatal Seizures**
1st choice: VPA	1st choice: ACTH, VGB,* VPA	1st choice: PB
2nd choice: TPM,LTG	2nd choice: TPM	2nd choice: PHT
3rd choice: ketogenic diet, VNS, ZNS, BZD, PB	3rd choice: LTG, TGB, BZD Consider: pyridoxine, ZNS, FBM	Consider: BZD, PRM, VPA, FBM, pyridoxine
Benign Epilepsy of Childhood With Centrotemporal Spikes (BECTS)		
1st choice: GBP, VPA, CBZ		
2nd choice: PHT		
3rd choice: PB, PRM, BZD		
Consider: TPM, LTG		

*Not available in the United States.

ACTH=adrenocorticotropic hormone; BZD=benzodiazepine; CBZ=carbamazepine; ESM=ethosuximide; FBM=felbamate; GBP=gabapentin; MTH=methsuximide; LEV=levetiracetam; LTG=lamotrigine; OXC=oxcarbazepine; PB=phenobarbital; PHT=phenytoin; PRM=primidone; TGB=tiagabine; TPM=topiramate; VGB=vigabatrin; VPA=valproic acid; ZNS=zonisamide

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result in good outcomes.[79] All women of childbearing age receiving AEDs should receive folate supplementation (at least 1 mg/d).[80]

Not only does discontinuation of therapy place mother and fetus at increased risk, but also it is unlikely to have much effect in terms of risk reduction, because in most cases the teratogenic drug is still present at the time the pregnancy is confirmed. Neural tube defects, including spina bifida, occur between 21 and 28 days after the last menstrual period; cleft lip occurs around day 35; and congenital heart defects occur with exposure before day 42 after the last menstrual period.[79]

Of the traditional AEDs, carbamazepine, with a 1% risk of neural tube defects, may be preferred to valproate, with a risk of neural tube defects of 2%. At the same time, carbamazepine, along with phenytoin and the barbiturates, reduces serum folate levels by as much as 90%. Current recommendations call for folate supplementation of 5 mg/d in pregnant women treated with either carbamazepine or valproate.[79] Information about teratogenicity associated with the newer AEDs is unavailable at this time.[78] Patients should be encouraged to participate in the management of their AED therapy. Also, pregnant women should be encouraged to participate in the Antiepileptic Drug Pregnancy Registry (1-800-233-2334) via the Internet at http://neuro-www2.mgh.harvard.edu/aed/registry.nclk so that more data can be gathered, especially for the newer AEDs.[78]

The safety of AEDs in breast-feeding is linked to the drug's protein-binding capacity; those AEDs that are highly

Table 18

AMERICAN ACADEMY OF NEUROLOGY QUALITY STANDARDS SUBCOMMITTEE RECOMMENDATIONS FOR WOMEN WITH EPILEPSY (WWE) DURING REPRODUCTIVE YEARS

Prepregnancy

- The choice of AED should be that deemed most appropriate for seizure types, ideally monotherapy
- Discuss potential for decreased effectiveness of hormonal contraception (HC) for WWE taking enzyme-inducing AEDs (eg, phenobarbital, primidone, phenytoin, topiramate [estrogen only], and carbamazepine)
- Folic acid supplementation with no less than 0.4 mg/d and continued through pregnancy; consider folic acid supplementation in any woman of childbearing potential
- Practice options:
  - For women taking enzyme-inducing AEDs, an HC formulation with at least 50 µg ethinyl estradiol or mestranol should be used
  - Prepregnancy counseling should be administered for women considering pregnancy and should include the following: teratogenic effects of AEDs, options for considering AED discontinuation before pregnancy, possibility of change in seizure frequency during pregnancy
- AED therapy should be optimized before conception if possible
- If AED withdrawal is planned, this should be completed at least 6 months before conception

During Pregnancy

- Change to an alternate AED should not be implemented during pregnancy for the sole purpose of reducing teratogenic risk
- WWE should be offered prenatal testing with α-fetoprotein levels at 14 to 16 weeks gestation and, if appropriate, amniocentesis for amniotic fluid α-fetoprotein and acetylcholinesterase levels
- Practice options:
  - Nonprotein-bound AED levels should be monitored during pregnancy
  - AED levels should be monitored through the 8th post-partum week
  - Vitamin K, 10 mg/d should be prescribed in the last month of pregnancy to WWE taking enzyme-inducing AEDs

Postpartum

- Breast-feeding is not contraindicated; however, monitor sedation of neonates of WWE taking sedating AEDs
- AED levels should be monitored through the 8th postpartum week.

Adapted with permission from Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: management of women with epilepsy (summary statement). *Neurology.* 1998;51:944-948.

protein-bound are less likely to be excreted into breast milk. The American Academy of Pediatrics has stated that women taking carbamazepine, valproate, or phenytoin can safely breast-feed.[79]

The Elderly

Acute and chronic seizures are commonly seen in adults older than 60 years of age. Etiology, presentation, treatment considerations, and long-term prognosis are substantially different in elderly patients with epilepsy than in younger adults. Seizures may present as altered mental status or memory lapses, and they can lead to a misdiagnosis of other medical disorders. Comorbid disorders such as neurodegenerative, cerebrovascular, or neoplastic disease are common.

The main issue of concern with elderly patients is the risk of drug interactions. A study of nearly 4300 nursing home residents taking AEDs found that many took concomitant medications with the potential for pharmacodynamic interactions. The classes of drugs included antidepressants, taken by 18.9%; antipsychotics, 12.7%; benzodiazepines, 22.4%; and thyroid supplements, 14.0%. Eleven percent were taking an adjunctive AED.[81]

Over-the-counter medications also may cause drug interactions. Some H_2-blockers (eg, cimetidine) are hepatic enzyme inhibitors, and some cold remedies, particularly those that contain decongestants, may increase seizures.

Elderly persons also experience changes in body composition and metabolism. Liver mass, blood flow, and hepatic clearance tend to decrease with age, potentially leading to increased concentration of AEDs. Doses of AEDs, especially those that inhibit hepatic enzymes, may need to be reduced.[81] Older patients may have decreased protein binding, leading to toxicity from elevated unbound AED concentrations. Therapy should be initiated at low doses, using once- or twice-daily dosing if possible, and titration should be made in small increments. Phenytoin is among the medications with the highest incidence of severe adverse effects among nursing home residents. Common drug interactions seen with AEDs include interactions with selective serotonin reuptake inhibitors, which inhibit phenytoin and carbamazepine, and induction interactions, which can affect the efficacy and toxicity of antipsychotics, antidepressants, and anticoagulants. Side effects from AEDs, such as gait disturbance, dizziness, and sedation, may have greater impact in patients who already have neurologic impairment. Weight gain and loss also are seen in many older patients taking AEDs. When selecting an AED, comorbid conditions, such as depression and obesity, and comedications such as anticoagulants that can cause potential drug interactions must be taken into account. The newer AEDs may have advantages over the older drugs, such as improved tolerability, fewer drug interactions, and less toxicity. Gabapentin and levetiracetam are important drugs to consider in the elderly as they lack hepatic metabolism and protein binding.

For elderly persons taking multiple prescription medications, cost also may be an issue, leading to possible noncompliance. The patient may be limited as to the number of drugs he or she can afford, eliminating one or more prescribed drugs at random. The clinician should take this into consideration and determine with the patient an appropriate course of action. Memory loss and visual impairment, common to elderly patients, can adversely affect compliance.

Epilepsy Surgery in Adults

Surgical therapy has been shown to be safe and effective for patients with medically refractory localization-related epilepsy. The rationale for surgical treatment is the excision of the epileptogenic zone. Favorable candidates for focal cortical resection include individuals with mesial temporal lobe epilepsy or seizures associated with a structural brain lesion. A recent randomized, controlled trial of epilepsy surgery showed that surgery was significantly more effective than continued medical treatment among patients with seizures resistant to several medications. The 1-year seizure-free rate was 58% for surgery and 8% for medical treatment. In addition, the only death in the trial was a patient randomized to continued medical treatment, showing that surgery has become a much safer treatment option.[1] The key elements of surgical candidacy are medically intractable epilepsy, a localized epileptogenic zone or site of seizure onset, and a low risk for new, postoperative neurologic deficits. The most common operative procedure involves resection of the epileptic brain tissue, typically the anterior temporal lobe.

The preoperative evaluation identifies the site of seizure onset and localizes functional cerebral cortex. It should include: extracranial ictal EEG and video monitoring, neuropsychometry, intracarotid amobarbital testing, and brain MRI, which reveals common pathologic alterations such as posttraumatic abnormalities, vascular malformation, tumor, disorders of cortical development, and MTS.

Most patients will require functional neuroimaging such as ictal SPECT, PET, or magnetic resonance spectroscopy (MRS). Intracranial EEG monitoring with subdural or depth electrodes is used when noninvasive studies fail to adequately localize the epileptogenic region or its proximity to motor, sensory, or language cortex.

The outcome of epilepsy surgery is variable and dependent on age of onset, location of the epileptic brain tissue, underlying pathology, and surgical strategy. Favorable prognostic indicators include early age of onset, mesial temporal lobe seizure onset, and pathologically identified MTS or foreign-tissue lesion. Less favorable operative candidates include patients with nonlesional extratemporal epilepsy. Surgical procedures achieve seizure freedom in 45% to 90% of individuals. More than 80% to 90% of patients with mesial temporal lobe or lesional epilepsy may become seizure-free or near seizure-free following total excision of the epileptogenic zone. The appropriate time for referral for surgical evaluation is unclear, but a recent survey suggested epileptologists will refer after three drugs (as monotherapy or combination therapy) fail to control seizures.

Epilepsy Surgery in Children

As with adults, surgical therapy for children is underutilized. The key elements of pediatric surgical candidacy are the same as for adults. Timing and a clearly defined purpose of the epilepsy surgery are critical components of the surgical evaluation. However, if a very young child is declining developmentally, there is urgency to perform surgery to maximize the potential for normal development. In very young children with catastrophic epilepsy, such as infantile spasms, who are candidates for surgery because of a localized lesion, the best opportunity for improved development is usually between 12 to 24 months of age and may be lost if surgery is delayed much beyond 30 months of age.

The most common etiologies of the epilepsies presenting for surgery in childhood are malformation of cortical development and low-grade tumor, although some patients with childhood-onset temporal lobe epilepsy due to hippocampal sclerosis also present early for surgery. In young patients with cortical dysplasia, the epilepsy may not be intractable and full control may be attained with medical treatment. Thus, surgery should not be considered until medical therapies have failed, even in children with a clearly defined focal cortical defect. Seizure types include medically intractable partial-onset seizures, partial-onset seizures associated with catastrophic childhood epilepsy (defined as being associated with mental retardation), and "generalized-onset" seizures associated with catastrophic childhood epilepsy, particularly infantile spasms or similar seizure disorders. Identification of a localized area of disturbance that is the cause of the child's seizures is often difficult. Four areas should be carefully examined: the history, the physical and neurologic examination, initial EEGs, and MRI findings.

Surgery can control medically intractable seizures and potentially alter the developmental course of children who otherwise may face lifelong mental retardation and perhaps institutionalization. Recent evidence suggests that seizures associated with certain epilepsy disorders can cause or significantly contribute to mental retardation. Infantile spasms, Rasmussen's encephalitis, and intractable seizures associated with Sturge-Weber syndrome and tuberous sclerosis are examples of such disorders. Several key factors define catastrophic childhood epilepsy, such as early onset, poor response to medications, and mental retardation. While few quantitative data are available, some anecdotal experience suggests that control of seizures by surgical relief may result in resumption of developmental progression, although the rate of development often remains abnormal. The best developmental outcomes are seen with earliest surgery and highest level of preoperative development.

Conclusion

The goal of epilepsy treatment is seizure freedom, but the consequences of epilepsy, such as diminished quality of life, prevention of disease progression, and the safety of AED therapy, also must be addressed. Continued research on disease prevention and modification, neuroprotection, and antiepileptogenesis will provide new information on how and when to use treatment interventions. Many of the newer AEDs have been proven to be effective in clinical trials, are better tolerated, and may provide safety advantages for a variety of patient populations. Often, selection of AED therapy is made on safety considerations, as well as the drug's spectrum of activity, especially in patients with unidentifiable or mixed seizure types.

If the newly diagnosed patient has partial-onset or localized seizures, it is likely that the first AED prescribed will be carbamazepine. In comparison studies against the standard AEDs, none of the newer AEDs has demonstrated clear superiority, although the newer AEDs typically have shown superior tolerability. All of the newer AEDs have been shown effective against partial-onset seizures, but head-to-head trials of the newer AEDs have not been performed. Topiramate and lamotrigine are noted for their broad spectrum of activity, including efficacy in the treatment of partial epilepsies, drop attacks, and tonic-clonic seizures in patients with Lennox-Gastaut syndrome; in addition, randomized clinical trials have shown topiramate to be efficacious in primary GTC seizures. If the patient has generalized-onset seizures, it is likely that valproate will be prescribed first. Of the newer AEDs, lamotrigine and topiramate also are effective in treating generalized-onset seizures.

The newer AEDs generally produce fewer adverse effects, in particular severe or idiosyncratic adverse effects, than the traditional AEDs. With regard to patient safety, the newer AEDs may have advantages over the traditional AEDs. With increasing experience with the newer AEDs, clinicians may prescribe one or another of them as a first-line drug. Of the newer AEDs, gabapentin and topiramate have no association with severe, life-threatening, or idiosyncratic adverse events and, although topiramate is a weak inducer of CYP450, neither AED is affected by drug interactions to any clinically important extent.

Special populations require special consideration. Children were once routinely treated with phenobarbital after an initial seizure. Many children may not require AED therapy after a first seizure, and when treatment is indicated, phenobarbital is not generally considered a drug of first choice except in the very young. When AED therapy is required, attention must be given to the different rates of metabolism and elimination and also to the increased susceptibility of children to cognitive side effects. Women of childbearing age need information and counseling. They should be dissuaded from discontinuing AED treatment when they become pregnant because the risk to themselves and to their unborn child may be equal or greater from uncontrolled seizures than from adverse AED effects. No drug has emerged as the AED of choice during pregnancy, and many years will be needed to accumulate data on the risk of teratogenesis with the newer AEDs. Comorbidities and concomitant therapies are important considerations when treating the elderly patient.

The molecular and cellular mechanisms of seizure activity and epilepsy are now being uncovered by basic research. The major direction for new therapeutic strategies will be to identify agents that are antiepileptogenic rather than anticonvulsant. The concept of disease modification in epilepsy is nearing a reality.

Decisions on when to start and withdraw AED therapy are based on accurate diagnosis and seizure classification, risk of recurrence, and assessment of seizure remission. Early identification of nonresponders and rapid seizure control define the approach to the patient who fails therapy with the first drug. In patients with refractory disease, vigorous efforts at seizure control with newer drugs that have less potential for drug interactions should be made. Referrals to epilepsy centers for evaluation should be made if therapy with two or three drugs fails. Epilepsy center evaluation can identify patients with nonepileptic events, classify epileptic seizures to guide treatment decisions, and identify potential epilepsy surgery candidates. Surgery is an effective and underutilized treatment for intractable seizures in adults and children and should be considered after failure of several medication trials using older and newer AEDs.

Future Directions in the Management of Epilepsy

The current management of epilepsy has goals that are far from simple to achieve. These include helping the patient attain a satisfactory quality of life by maintaining effective seizure control. The introduction of new AEDs in the past decade has increased the likelihood of attaining these goals for more patients.

The genetic components of the many idiopathic epilepsies and the development of interventions that prevent genetic susceptibilities from developing into full-blown epilepsies represent exciting areas of research that may hold promise in the future. Genetic screening may help guide AED choice and predict idiosyncratic adverse events.

As with adults, surgical therapy is underutilized in children. The key elements for surgical candidacy for both adults and children are the same: medically intractable epilepsy, a localized epileptogenic zone or site of seizure onset, and a low risk for new, postoperative neurologic deficits. Surgical therapy may be a safe and effective option for patients with certain kinds of hard to control seizures that do not respond well to treatment with anticonvulsant drugs. Advances in brain imaging have allowed earlier identification of optimal surgical candidates.

The likelihood of a "cure" for epilepsy is difficult to assess. Some seizure types respond relatively well to treatment, and patients can attain seizure freedom and remain seizure-free for life, even after discontinuing AEDs, while others have seizures that are refractory to treatment. Nevertheless, as the understanding of neural circuits and neurotransmitter systems improves, interventions may be discovered that affect epileptogenesis in such a way as to achieve seizure freedom for all patients and even prevent epilepsy in susceptible populations before it appears.

References

1. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med.* 2001;345(5):311-318.
2. Manford M, Hart YM, Sander JW, Shorvon SD. The National General Practice Study of Epilepsy. The syndromic classification of the International League Against Epilepsy applied to epilepsy in a general population. *Arch Neurol.* 1992;49(8):801-808.
3. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. *Lancet.* 2000;356(9226):323-329.
4. Kolodny EH. Metabolic and genetic disorders. In: Devinsky O, Westbrook L, eds. *Epilepsy and Developmental Disabilities: Causes and Consequences.* Woburn, Ma: Butterworth-Heinemann. 2001:17-22.
5. Loscher W. Pharmacology of glutamate receptor antagonists in the kindling model of epilepsy. *Prog Neurobiol.* 1998;54(6):721-741.
6. Stefani A, Spadoni F, Bernardi G. Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia.* 1997;38(9):959-965.
7. Hauser WA. Seizure disorders: the changes with age. *Epilepsia.* 1992;33(suppl 4):S6-14.
8. Sanchez RM, Jensen FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. *Epilepsia.* 2001;42(5):577-585.
9. Annegers JF. The epidemiology of epilepsy. In: Wyllie JE, eds. *The Treatment of Epilepsy: Principles and Practices.* Philadelphia, Pa:Lea & Febiger; 1993:157-164.
10. Hauser WA, Olafsson E, Ludvigsson P. *Epilepsia.* 1997;38(suppl 8):136.
11. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. *Epilepsia.* 1996;37(3):224-229.
12. Sidenvall R, Forsgren L, Blomquist HK, Heijbel J. A community-based prospective incidence study of epileptic seizures in children. *Acta Paediatr.* 1993;82(1):60-65.
13. Hessdorffer DC. Risk factors. In: Engle J Jr, Pedley TA, eds. Epilepsy: A Comprehensive Textbook. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:59-76.
14. Langan Y. Sudden unexpected death in epilepsy (SUDEP): risk factors and case control studies. *Seizure.* 2000;9(3):179-183.
15. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia.* 1997;38(3):353-362.
16. Foldvary N, Wylie E. Epilepsy. In: Goetz CG, Pappert E, eds. *Textbook of Clinical Neurology.* Philadelphia, Pa: WB Saunders Co; 1999:1059-1088.
17. McGugan EA. Sudden unexpected deaths in epileptics--a literature review. *Scott Med J.* 1999;44(5):137-139.
18. Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology.* 1998;51(5):1270-1274.
19. Tomson T. Mortality in epilepsy. *J Neurol.* 2000;247(1):15-21.
20. Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia.* 2000;41(5):549-553.
21. Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, et al. The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. *Epilepsy Res.* 2000;41(1):39-51.
22. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK. Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology.* 1999;53(1):162-166.
23. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, Coan S, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia.* 2000;41(3):342-351.
24. Panayiotopoulos CP. Diagnosis in epilepsies: still a central problem? *Eur J Neurol.* 1996;3(suppl 3):3-8.
25. Cascino GC. Structural brain imaging. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia, Pa: Lippincott-Raven Publishers; 1997:937-946.
26. Henry TR, Chugani HT. Positron emission tomography. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia, Pa: Lippincott-Raven Publishers; 1997:937-946.

27. Generalised idiopathic epilepsies. Available at: http://www.mynchen.demon.co.uk. Accessed on March 13, 2002.
28. Atakli D, Sozuer D, Atay T, Baybas S, Arpaci B. Misdiagnosis and treatment in juvenile myoclonic epilepsy. *Seizure.* 1998;7(1):63-66.
29. Grunewald RA, Chroni E, Panayiotopoulos CP. Delayed diagnosis of juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry.* 1992;55(6):497-499.
30. Benbadis SR. Observations on the misdiagnosis of generalized epilepsy as partial epilepsy: causes and consequences. *Seizure.* 1999;8(3):140-145.
31. Dulac O, Leppik IE. Initiating and discontinuing treatment. In: Engle J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia, Pa: Lippincott-Raven Publishers; 1997:1237-1246.
32. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med.* 1998;338(7):429-434.
33. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology.* 1998;51(5): 1256-1262.
34. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? *Seizure.* 2000;9(7):464-468.
35. Richens A. Rational polypharmacy. *Seizure.* 1995;4(3):211-214.
36. Johannessen S, Henriksen O. Maintenance therapy. In: Engle J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia, Pa: Lippincott-Raven Publishers; 1997:1247-1253.
37. Beydoun A. Monotherapy trials of new antiepileptic drugs. *Epilepsia.* 1997; 38(suppl 9):S21-31.
38. Cramer JA, Fisher R, Ben-Menachem E, French J, Mattson RH. New antiepileptic drugs: comparison of key clinical trials. *Epilepsia.* 1999;40(5):590-600.
39. Privitera MD, Brodie JM, Neto W, Wang S. Topiramate vs. investigator choice of carbamazepine or valproate as monotherapy in newly diagnosed epilepsy. *Epilepsia.* 2000;41(suppl 7):93. Abstract 2.019.
40. Chadwick D, Leiderman DB, Sauermann W, Alexander J, Garofalo E. Gabapentin in generalized seizures. *Epilepsy Res.* 1996;25(3):191-197.
41. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet.* 1995;345(8948):476-479.
42. Greenwood RS. Adverse effects of antiepileptic drugs. *Epilepsia.* 2000;41(suppl 2):S42-52.
43. Glauser TA. Idiosyncratic reactions: new methods of identifying high-risk patients. *Epilepsia.* 2000;41(suppl 8):S16-29.
44. Genton P, Van Vleymen B. Piracetam and levetiracetam: close structural similarities but different pharmacological and clinical profiles. *Epileptic Disord.* 2000;2(2):99-105.
45. Elger CE, Bauer J, Scherrmann J, Widman G. Aggravation of focal epileptic seizures by antiepileptic drugs. *Epilepsia.* 1998;39(suppl 3):S15-18.
46. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia.* 1998;39(1):5-17.
47. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia.* 1997;38(8):859-880.
48. Handforth A, DeGiorgio CM, Schachter SC. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology.* 1998;51(1):48-55.
49. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures: results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. *Arch Neurol.* 1996;53(11):1176-1180.
50. Privitera MD, Szaflarski JP. Complex partial seizures in adults. *Curr Treat Options Neurol.* 1999;1(4):323-338.
51. The Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). *N Engl J Med.* 1993;328(1):29-33.
52. Pellock JM. Felbamate. *Epilepsia.* 1999;40(suppl 5):S57-62.
53. Brodie MJ, Pellock JM. Taming the brain storms: felbamate updated. *Lancet.* 1995;346(8980):918-919.
54. *Physician's Desk Reference.* 55th ed. Montvale, NJ: Medical Economics Co. 2001.
55. McLean MJ. Gabapentin in the management of convulsive disorders. *Epilepsia.* 1999;40(suppl 6):S39-50; discussion S73-34.
56. Morrell MJ. Dosing to efficacy with neurontin: the STEPS trial. Study of Titration to Effect Profile of Safety. *Epilepsia.* 1999;40(suppl 6):S23-26; discussion S73-24.
57. Wong IC, Lhatoo SD. Adverse reactions to new anticonvulsant drugs. *Drug Saf.* 2000;23(1):35-56.
58. Mechatie E. *Clinical Psychiatry News.* 2000;28(6):5.
59. Leppik IE. Zonisamide. *Epilepsia.* 1999;40(suppl 5):S23-29.
60. Steiner TJ, Silveria C, Yuen AWC. Comparison of lamotrigine (Lamictal) and phenytoin monotherapy in newly diagnosed epilepsy. *Epilepsia.* 1994;35(suppl 7):61.
61. Chang G, Vasquez B, Gilliam F, et al. Lamictal (lamotrigine) monotherapy is an effective treatment for partial seizures. *Neurology.* 1997;48(suppl 2):A335. Abstract.
62. Ayala R, Casale EJ, Brookins TA. The effectiveness and safety of Lamictal (lamotrigine) monotherapy for the treatment of newly-diagnosed typical absence seizures in children and adolescents. *Epilepsia.* 1996;37(suppl 5):165. Abstract.
63. Lamictal Prescribing Information. Glaxo SmithKline; Reserach Triangle Park, NC. 2001.
64. Hovinga CA. Levetiracetam: a novel antiepileptic drug. *Pharmacotherapy.* 2001;21(11):1375-1388.
65. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology.* 2000;55(2):236-242.
66. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia.* 2000;41(9):1179-1186.
67. Glauser TA. Oxcarbazepine in the treatment of epilepsy. *Pharmacotherapy.* 2001;21(8): 904-919.
68. Eckardt KM, Steinhoff BJ. Nonconvulsive status epilepticus in two patients receiving tiagabine treatment. *Epilepsia.* 1998;39(6):671-674.
69. Knake S, Hamer HM, Schomburg U, Oertel WH, Rosenow F. Tiagabine-induced absence status in idiopathic generalized epilepsy. *Seizure.* 1999;8(5):314-317.
70. Buck ML. Topiramate for the management of seizures in children. *Pediatr Pharmacother.* 2001;7(6).
71. Faught E. Clinical studies of topiramate. *Drugs of Today.* 1999;35:49-57.
72. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia.* 2000;41(suppl 1):S3-9.
73. Guberman A. Efficacy of 200 mg/day topiramate in treatment-resistant partial seizures when added to an enzyme-inducing drug (AED). *Epilepsia.* 2001;42(suppl 7):179-180.
74. Naritoku DK, Hulihan J, Kamin M, et al. Reduction of antiepileptic drug (AED) co-therapy improves tolerability of add-on therapy with topiramate: a novel randomized study. *Epilepsia.* 2001;42(suppl 6):258-259.
75. Camfield PR, Camfield CS. Treatment of children with “ordinary” epilepsy. *Epileptic Disord.* 2000;2(1):45-51.
76. Roste LS, Tauboll E, Berner A, Isojarvi JI, Gjerstad L. Valproate, but not lamotrigine, induces ovarian morphological changes in Wistar rats. *Exp Toxicol Pathol.* 2001;52(6):545-552.
77. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia.* 1997;38(3):317-323.
78. Chang SI, McAuley JW. Pharmacotherapeutic issues for women of childbearing age with epilepsy. *Ann Pharmacother.* 1998;32(7-8):794-801.
79. Nulman I, Laslo D, Koren G. Treatment of epilepsy in pregnancy. *Drugs.* 1999;57(4): 535-544.
80. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: management issues for women with epilepsy (summary statement). *Neurology.* 1998;51(4):944-948.
81. Lackner TE, Cloyd JC, Thomas LW, Leppik IE. Antiepileptic drug use in nursing home residents: effect of age, gender, and comedication on patterns of use. *Epilepsia.* 1998;39(10):1083-1087.

POST-TEST, PROGRAM EVALUATION, AND CME CREDIT REQUEST

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati College of Medicine and SynerMed Communications.

The University of Cincinnati College of Medicine designates this educational activity for a maximum of 3 hours in Category 1 credit towards the AMA Physician's Recognition Award (PRA). Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

To apply for Category 1 credit, you must:

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Each participant achieving a grade of 70% or higher on the examination will receive documentation of CME credit hours earned. Participants receiving a grade of less than 70% on the exam will be notified and permitted to take one reexamination at no additional cost.

Please complete the statement with the most correct word, phrase, or figure.

1. In the study by Manford (1992), the ILAE classification scheme was able to place approximately ______ of patients with epilepsy in diagnostic ILAE categories. The remainder were in nonspecific categories.
   a. 80% c. 33%
   b. 50% d. 20%

2. The method of choice in visualizing lesions such as small tumors, cortical dysgenesis, or mesial temporal sclerosis is ______.
   a. CT c. PET
   b. MRI d. SPECT

3. Traditional AEDs primarily affect these targets: ______ and ______.
   a. Na+ and Ca++ channel inhibition
   b. Na+ channel and glutamatergic inhibition
   c. Na+ channel and GABA transmission inhibition
   d. Na+ channel inhibition and GABA transmission increase

4. For all age cohorts, ______ of epilepsies are of unknown origin.
   a. 33% c. 65%
   b. 40% d. 80%

5. The most common type of seizures in pediatric patients is ______.
   a. Generalized tonic-clonic seizures
   b. Simple partial seizures
   c. Complex partial seizures
   d. None of the above

6. The risk factor for epilepsy with the highest odds ratio is ______.
   a. Cerebrovascular accident
   b. Alzheimer's disease
   c. Brain tumor
   d. Military head injury

7. The incidence of sudden unexplained death in persons with epilepsy is ______ times higher than the incidence of sudden unexplained death in the general population.
   a. 6 c. 24
   b. 12 d. 48

8. According to a survey (Fisher, 2000) of more than 1000 people in two community-based samples, approximately ______ persons with epilepsy were employed full-time and ______ were unemployed.
   a. One half; one fourth
   b. One fourth; one fourth
   c. One fourth; one half
   d. One half; one half

9. The risk of seizure recurrence increases after a second or third unprovoked seizure; ______ of persons who have had two or three unprovoked seizures will go on to have additional seizures.
   a. 75% b. 60% c. 45% d. 30%

10. In the study by Kwan and Brodie, the percentage of patients who achieved seizure freedom with monotherapy with a second AED after failure of a first AED was __________.
    a. 36% b. 27% c. 18% d. 9%

11. Seizure frequency tends to increase during pregnancy; in fact, ______ to ______ of women sustain more seizures during pregnancy.
    a. 20% to 50% c. 49% to 56%
    b. 23% to 46% d. None of the above

12. Important advantages of the newer AEDs over the older AEDs are:
    a. Broader spectrum of activity for most, if not all, agents
    b. Fewer drug interactions
    c. Fewer serious adverse effects
    d. All of the above

13. In the analysis of Marson et al, the newer AED with the highest odds ratio for response in terms of the percentage of patients achieving a 50% reduction in seizure occurrence is ______.
    a. Gabapentin c. Oxcarbazepine
    b. Topiramate d. Zonisamide

14. The newer AEDs with little association with severe, life-threatening, or idiosyncratic side effects are ______ and ______.
    a. Felbamate and tiagabine
    b. Gabapentin and lamotrigine
    c. Topiramate and zonisamide
    d. Gabapentin and topiramate

PROGRAM EVALUATION

The University of Cincinnati College of Medicine would appreciate your comments regarding the quality of the information presented, and thanks you for your participation.

1. The program objectives were fully met.
   a. Strongly agree b. Agree
   c. Disagree d. Strongly disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   a. Strongly agree b. Agree
   c. Disagree d. Strongly disagree

3. The educational activity has enhanced my professional effectiveness and improved my ability to:
   a. Treat/manage patients
      a. Strongly agree b. Agree c. Disagree
      d. Strongly disagree e. Nonapplicable
   b. Communicate with patients
      a. Strongly agree b. Agree c. Disagree
      d. Strongly disagree e. Nonapplicable
   c. Manage my medical practice
      a. Strongly agree b. Agree c. Disagree
      d. Strongly disagree e. Nonapplicable

4. The information presented was without promotional or commercial bias.
   a. Strongly agree b. Agree
   c. Disagree d. Strongly disagree

5. The program level was appropriate.
   a. Strongly agree b. Agree
   c. Disagree d. Strongly disagree

6. Do you intend to change your clinical practice as a result of the information presented in this CME program?
   Yes No
   Comments:______________________________

7. How long did it take you to complete this activity?
   ____

8. Suggestions regarding this material, or recommendations for future presentations:
   ____
   ____
   ____

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Deadline for receipt of the completed Post-Test/Self-Assessment and Program Evaluation is March 2004.

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Developed and Produced by
SynerMed Communications